US010407419B2

(12) **United States Patent**
Lin et al.

(10) **Patent No.: US 10,407,419 B2**
(45) **Date of Patent: *Sep. 10, 2019**

(54) **QUINOLINONE FIVE-MEMBERED HETEROCYCLIC COMPOUNDS AS MUTANT-ISOCITRATE DEHYDROGENASE INHIBITORS**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **15/568,072**

(22) PCT Filed: **Sep. 18, 2015**

(86) PCT No.: **PCT/US2015/051059**

§ 371 (c)(1),
(2) Date: **Oct. 20, 2017**

(87) PCT Pub. No.: **WO2016/171756**

PCT Pub. Date: **Oct. 27, 2016**

(65) **Prior Publication Data**

US 2018/0118732 A1 May 3, 2018

Related U.S. Application Data

(60) Provisional application No. 62/150,816, filed on Apr. 21, 2015.

(51) **Int. Cl.**

C07D 417/12	(2006.01)
C07D 417/14	(2006.01)
C07D 471/04	(2006.01)
A61P 35/00	(2006.01)

(52) **U.S. Cl.**

CPC ***C07D 417/12*** (2013.01); ***A61P 35/00*** (2018.01); ***C07D 417/14*** (2013.01); ***C07D 471/04*** (2013.01)

(58) **Field of Classification Search**

None

See application file for complete search history.

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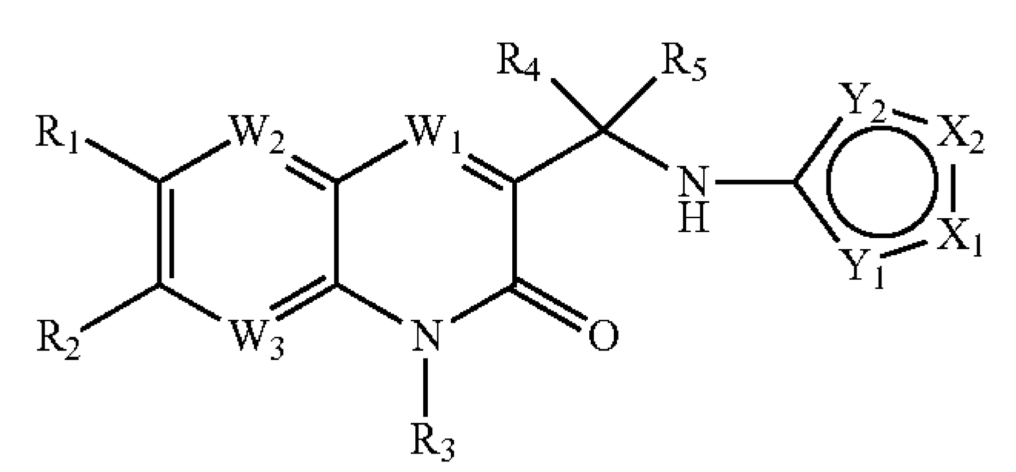
(57) **ABSTRACT**

The invention relates to inhibitors of mutant isocitrate dehydrogenase (mt-IDH) proteins with neomorphic activity useful in the treatment of cell-proliferation disorders and cancers, having the Formula: (I) where Y_1, X_1, X_2, Y_2, W_1, W_2, W_3, and R_1-R_5 are described herein.

(I)



5 Claims, 1 Drawing Sheet

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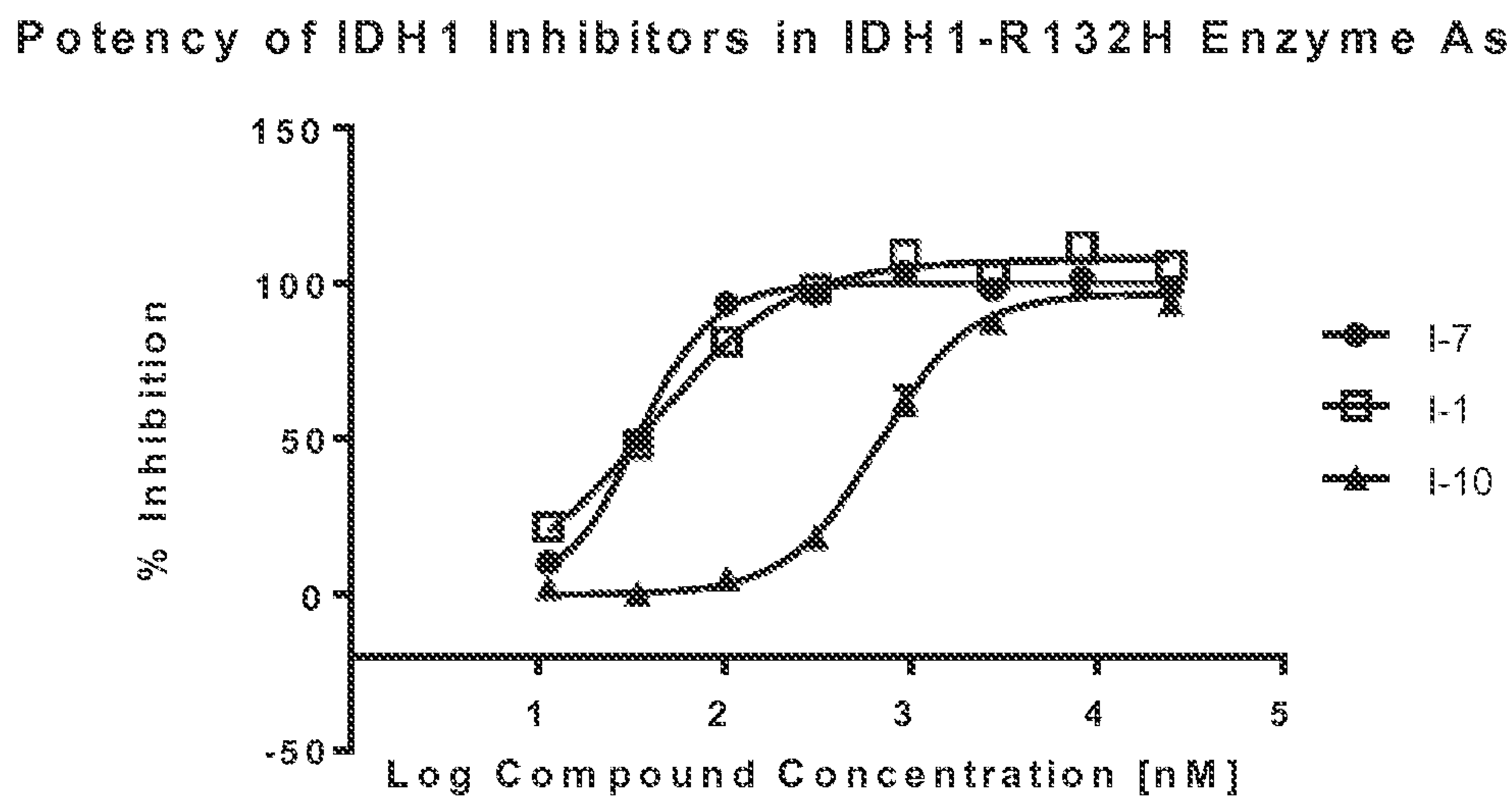


Cpd No	IC_{50} (nM)
I-1	39.84
I-7	34.02
I-10	673.40

QUINOLINONE FIVE-MEMBERED HETEROCYCLIC COMPOUNDS AS MUTANT-ISOCITRATE DEHYDROGENASE INHIBITORS

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a National Stage Entry of PCT/US2015/051059, filed Sep. 18, 2015, which claims the benefit of priority of U.S. Provisional Application No. 62/150,816, filed Apr. 21, 2015, all of which is incorporated herein by reference in its entirety.

FIELD OF INVENTION

The present invention is directed to inhibitors of mutant iso citrate dehydrogenase (mt-IDH) proteins with neomorphic activity useful in the treatment of diseases or disorders associated with such mutant IDH proteins including cell-proliferation disorders and cancers. Specifically, the invention is concerned with compounds and compositions inhibiting mt-IDH, methods of treating diseases or disorders associated with mt-IDH, and methods of synthesis of these compounds.

BACKGROUND OF THE INVENTION

Isocitrate dehydrogenases (IDHs) are enzymes that participate in the citric acid cycle (cellular metabolism). They catalyze the oxidative decarboxylation of isocitrate to 2-oxoglutarate (i.e., α-ketoglutarate, α-KG). There are three isoforms within the IDH family. IDH-1, expressed in the cytoplasm and peroxisome, IDH-2, localized in the mitochondria, both utilize $NADP^+$ as the cofactor and exist as homodimers. IDH-3 is localized in mitochondrial matrix and utilizes NAD^+ as a cofactor and exists as tetramer. Mutations in IDH-1 (cytosolic) and IDH-2 (mitochondrial) have been identified in various diseases or disorders including glioma, glioblastoma multiforme, paraganglioma, supratentorial primordial neuroectodermal tumors, acute myeloid leukemia (AML), prostate cancer, thyroid cancer, colon cancer, chondrosarcoma, cholangiocarcinoma, peripheral T-cell lymphoma, and melanoma (L. Deng et al., *Trends Mol. Med.,* 2010, 16, 387; T. Shibata et al., *Am. J. Pathol.,* 201 1, 178 (3), 1395; Gaal et al., *J. Clin. Endocrinol. Metab.* 2010; Hayden et al., *Cell Cycle,* 2009; Balss et al., *Acta Neuropathol.,* 2008). The mutations have been found at or near key residues in the active site: G97D, R100, R132, H133Q, and A134D for IDH1, and R140 and R172 for IDH2. (See L. Deng et al., *Nature,* 2009, 462, 739; L. Sellner et al., *Eur. J. Haematol.,* 2011, 85, 457).

Mutant forms of IDH-1 and IDH-2 have been shown to lose wild type activity, and instead exhibit a neomorphic activity (also known as a gain of function activity), of reducing alpha-ketoglutarate to 2-hydroxyglutarate (2-HG). (See P. S. Ward et al., *Cancer Cell,* 2010, 17, 225; Zhao et. al., Science 324, 261 (2009); Dang et. al Nature 462, 739 (2009)). In general, production of 2-HG is enantiospecific, resulting in generation of the D-enantiomer (also known as the R enantiomer or R-2-HG). Normal cells have low basal levels of 2-HG, whereas cells harboring mutations in IDH1 or IDH2 show significantly elevated levels of 2-HG. High levels of 2-HG have also been detected in tumors harboring the mutations. For example, high levels of 2-HG have been detected in the plasma of patients with mutant IDH containing AML. (See S. Gross et al., *J. Exp. Med.,* 2010, 207 (2),

339). High levels of 2-HG have been shown to block α-KG dependent DNA and histone demethylases, and ultimately to result in improper dedifferentiation of hematopoietic progenitor cells in AML patients (Wang et. al., Science 340, 622 (2013); Losman et al., Science 339, 1621 (2013)).

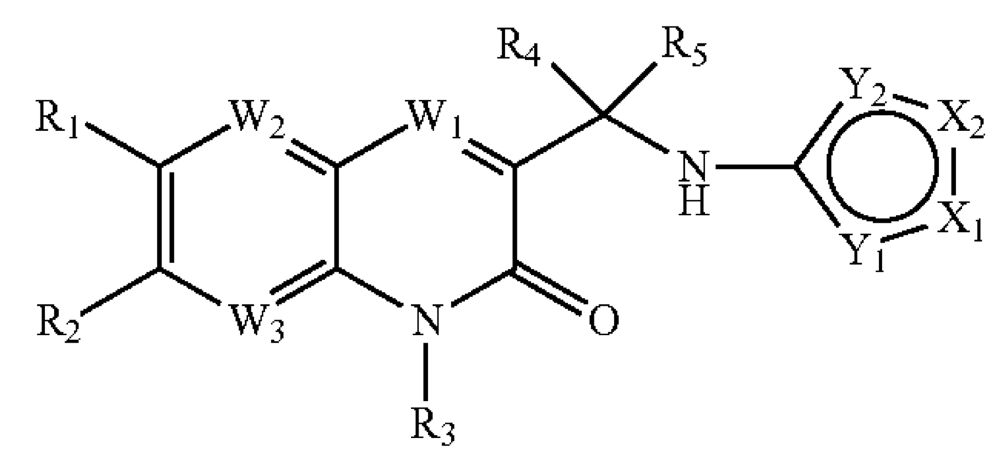
Furthermore, patients with Oilier Disease and Mafucci Syndrome (two rare disorders that predispose to cartilaginous tumors) have been shown to be somatically mosaic for IDH1 and 2 mutations and exhibit high levels of D-2-HG. (See Amary et al., *Nature Genetics,* 2011 and Pansuriya et al., *Nature Genetics,* 2011).

The inhibition of mt-IDHs and their neomorphic activity with small molecule inhibitors therefore has the potential to be a treatment for cancers and other disorders of cellular proliferation.

SUMMARY OF THE INVENTION

A first aspect of the invention relates to compounds of Formula (I):

(I)



and pharmaceutically acceptable salts, enantiomers, hydrates, solvates, prodrugs, isomers, and tautomers thereof, wherein:

each W_1 and W_2 is independently CH, CF, or N;

W_3 is independently CR_2, or N;

Y_1, X_1, X_2, and Y_2 are independently at each occurrence selected from CR_6, CR_6', N, $NR_{6'}$, O, or S, provided that the ring containing Y_1, X_1, X_2, and Y_2 cannot have more than 4 N or NH atoms nor more than one S or O atoms, wherein the S and O are not contiguous;

R_1 is independently H, OH, CN, halogen, CF_3, CHF_2, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, 3- to 8-membered heterocyclyl, aryl, or heteroaryl, wherein each C_1-C_6 alkyl, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, 3- to 8-membered heterocyclyl, aryl, or heteroaryl is optionally substituted one or more times with substituents selected from the group consisting of halogen, OH, NH_2, CN, C_1-C_6 alkyl, and C_1-C_6 alkoxy;

each R_2 is independently H, OH, CN, halogen, CF_3, CHF_2, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, 3- to 8-membered heterocyclyl, aryl, heteroaryl, NH_2, —$O(CH_2)R_7$, —$O(CH_2)C(O)NHR_7$, —$O(CH_2)_nC(O)R_7$, NHR_7, —$N(R_7)(R_8)$, $NHC(O)R_7$, $NHS(O)R_7$, $NHS(O)_2R_7$, $NHC(O)OR_7$, $NHC(O)NHR_7$, —$S(O)_2NHR_7$, $NHC(O)N(R_8)R_7$, —OCH_2R_7, —$OCHR_7R_8$, or —CHR_7R_8, wherein C_1-C_6 alkyl or C_1-C_6 alkoxy is optionally substituted with one or more substituents selected from the group consisting of C_1-C_6 alkyl, C_1-C_6 alkoxy, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_3-C_8 halocycloalkyl, 3- to 8-membered heterocyclyl, aryl, -heteroaryl-$C(O)NH_2$, and heteroaryl;

R_3 is H or C_1-C_6 alkyl;

R_4 and R_5 are independently H, halogen, CH_2OH, C_1-C_3 alkyl, or C_1-C_3 alkyl substituted with halogen, or R_4 and R_5 when combined can form a C_3-C_6 cycloalkyl or C_3-C_6 heterocyclyl;

R_6 and R_6', at each occurrence, are each independently selected from the group consisting of H, OH, CN, —CH_2CN, C_1-C_6 alkyl, —$O(CH_2)C(O)NHR_7$, —$O(CH_2)C(O)R_7$, NHR_7, —$N(R_7)(R_8)$, —$NHC(O)R_7$, —$NHS(O)R_7$, —$NHS(O)_2R_7$, —$NHC(O)OR_7$, —$NHC(O)NHR_7$, —$S(O)_2NHR_7$, —$NHC(O)N(R_8)R_7$, —OCH_2R_7, $R_7NHC(O)$—, $R_7S(O)_2$—, C_1-C_6 alkoxy, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl, 3- to 8-membered heterocyclyl, aryl, and heteroaryl, wherein each alkyl, C_1-C_6 alkoxy, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkyl, 3- to 8-membered heterocyclyl, aryl, and heteroaryl are optionally substituted with one or more substituents selected from the group consisting of OH, halogen, oxo, thioxo, C_1-C_6 alkoxy, C_1-C_6 alkyl. C_1-C_6 haloalkyl, NH_2, CN, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkylalkyl, 3- to 8-membered heterocyclyl, aryl, heteroaryl, and $R_7S(O)_2$—

or two of R_6, or R_6 and R_6', when adjacent, can be taken together to form an aryl, a 5 to 8-membered heterocyclyl, or 5 to 6-membered heteroaryl, wherein the heterocylcyl or heteroaryl is further optionally substituted with one or more substituents selected from the group consisting of H, OH, CN, oxo, —$COOR_7$, —CH_2CN, C_1-C_6 alkyl, $R_7S(O)_2$—, C_1-C_6 alkoxy, C_2-C_6 alkenyl, C_2-C_6 alkenyl, C_3-C_8 cycloalkyl, C_3-C_8 cycloalkylalkyl, 3- to 8-membered heterocyclyl, aryl, and heteroaryl;

R_7 and R_8 are each independently H, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_2-C_6 alkenyl, C_2-C_6 alkynyl, C_3-C_8 cycloalkyl, 3- to 8-membered heterocyclyl, aryl, and heteroaryl; or when combined R_7 and R_8 can form a 3- to 8-membered heterocyclyl or heteroaryl ring; and

n is an integer from 0 to 3;

provided that:

(1) the compound is not 3-((thiazol-2-ylamino)methyl)quinolin-2(1H)-one; or

(2) R_1, R_2, R_3, R_4, R_5, R_6, and R_6' are not all simultaneously H.

Another aspect of the invention relates to a method of treating a disease or disorder associated with mutant isocitrate dehydrogenase. The method comprises administering to a patient in need of a treatment for diseases or disorders associated with mutant isocitrate dehydrogenase an effective amount of a compound of Formula (I).

Another aspect of the invention is directed to a method inhibiting mutant isocitrate dehydrogenase. The method involves administering to a patient in need thereof an effective amount of a compound of Formula (I).

Another aspect of the invention relates to method of reducing 2-hydroxyglutarate. The method comprises administering to a patient in need thereof an effective amount of a compound of Formula (I).

Another aspect of the invention is directed to pharmaceutical compositions comprising a compound of Formula (I) and a pharmaceutically acceptable carrier. The pharmaceutically acceptable carrier may further include an excipient, diluent, or surfactant.

The present invention further provides methods of treating cell proliferative diseases and cancers including, without limitation, glioma, glioblastoma multiforme, paraganglioma, supratentorial primordial neuroectodermal tumors, acute myeloid leukemia (AML), prostate cancer, thyroid cancer, colon cancer, chondrosarcoma, cholangiocarcinoma, peripheral T-cell lymphoma, melanoma, intrahepatic cholangiocarcinoma (IHCC), myelodysplastic syndrome (MDS), myeloproliferative disease (MPD), and other solid tumors, comprising administering to a patient suffering from at least one of said diseases or cancers a compound of Formula (I). The inhibitors of the present invention may target mutated IDH1 at residue 97, 100 or 132, for example G97D, R100Q, R132H, R132C, R132S, R132G, R132L, and R132V. The inhibitors of the present invention may target mutated IDH2 at residue 140 or 172, for example R140Q, R172K, R172M, R172S, R172G, and R172W.

Another aspect of the invention provides for a compound of Formula (I), or a pharmaceutically acceptable salt thereof, in combination with another therapeutic agent.

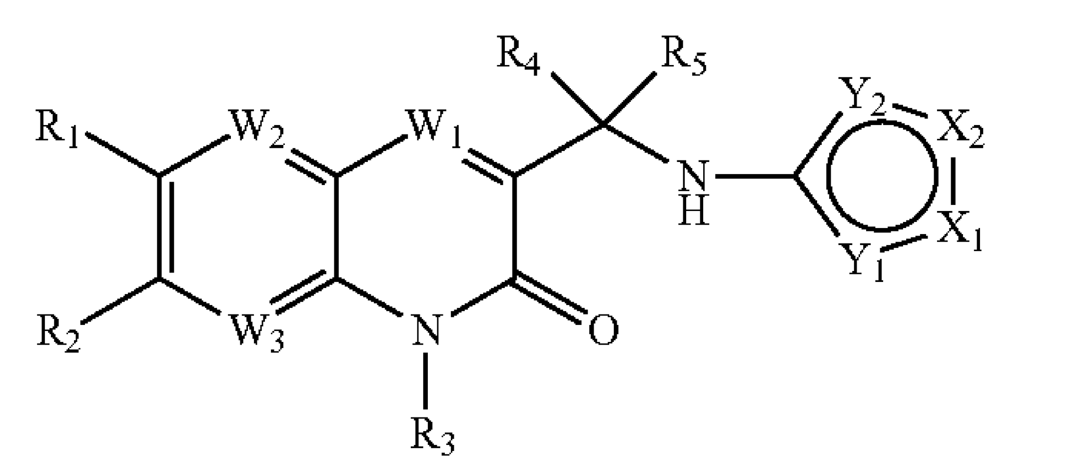
BRIEF DESCRIPTION OF THE DRAWINGS OF THE INVENTION

FIG. **1** illustrates a graph showing the potency of IDH1 inhibitors in IDH1-132H enzyme assay.

DETAILED DESCRIPTION OF THE INVENTION

IDH1 or IDH2 mutations are a genetically validated target in many solid and hematologic cancers, but there are currently no targeted therapies available for patients in need of treatment for specific conditions associated with mt-IDH activity. Non-mutant IDH (e.g., wild-type) catalyze the oxidative decarboxylation of isocitrate to α-ketoglutarate thereby reducing NAD^+ (NADP) to NADH (NADPH) (WO 2013/102431 to Cianchetta et al., hereby incorporated by reference in its entirety). Mutations of IDH present in certain cancer cells result in a new ability of the enzyme to catalyze the NADPH-dependent reduction of α-ketoglutarate R(−)-2-hydroxyglutarate (2HG). 2HG is not formed by wild-type IDH. The production of 2HG contributes to the formation and progression of cancer (Dang, L et al., Nature, 2009, 462:739-44, hereby incorporated by reference in its entirety). The present invention provides inhibitors of mt-IDH, and prophylactic measures to reduce the formation and progression of 2HG in cells.

In a first aspect of the invention, are described the compounds of Formula (I):



(I)

and pharmaceutically acceptable salts, enantiomers, hydrates, solvates, prodrugs, isomers, and tautomers thereof, where Y_1, X_1, X_2, Y_2, W_1, W_2, W_3, and R_1-R_5 are described as above.

The details of the invention are set forth in the accompanying description below. Although methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, illustrative methods and materials are now described. Other features, objects, and advantages of the invention will be apparent from the description and from the claims. In the specification and the appended claims, the singular forms also include the plural unless the context clearly dictates otherwise. Unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. All patents and publications cited in this specification are incorporated herein by reference in their entireties.

Definitions

The articles "a" and "an" are used in this disclosure to refer to one or more than one (i.e., to at least one) of the grammatical object of the article. By way of example, "an element" means one element or more than one element.

The term "and/or" is used in this disclosure to mean either "and" or "or" unless indicated otherwise.

The term "optionally substituted" is understood to mean that a given chemical moiety (e.g. an alkyl group) can (but is not required to) be bonded other substituents (e.g. heteroatoms). For instance, an alkyl group that is optionally substituted can be a fully saturated alkyl chain (i.e. a pure hydrocarbon). Alternatively, the same optionally substituted alkyl group can have substituents different from hydrogen. For instance, it can, at any point along the chain be bounded to a halogen atom, a hydroxyl group, or any other substituent described herein. Thus the term "optionally substituted" means that a given chemical moiety has the potential to contain other functional groups, but does not necessarily have any further functional groups. Suitable substituents used in the optional substitution of the described groups include, without limitation, halogen, oxo, CN, —COOH, —CH_2CN, —O—C_1-C_6alkyl, C_1-C_6alkyl, —OC_1-C_6alkenyl, —OC_1-C_6alkynyl, —C_1-C_6alkenyl, —C_1-C_6alkynyl, —OH, —OP(O)$(OH)_2$, —OC(O)C_1-C_6alkyl, —C(O)C_1-C_6alkyl, —OC(O)OC_1-C_6alkyl, NH_2, NH(C_1-C_6alkyl), N(C_1-C_6alkyl$)_2$, —NHC(O)C_1-C_6alkyl, —C(O)NHC_1-C_6alkyl, —S(O)$_2$—C_1-C_6alkyl, —S(O)NHC_1-C_6alkyl, and S(O)N(C_1-C_6 alkyl$)_2$

Unless otherwise specifically defined, the term "aryl" refers to cyclic, aromatic hydrocarbon groups that have 1 to 2 aromatic rings, including monocyclic or bicyclic groups such as phenyl, biphenyl or naphthyl. Where containing two aromatic rings (bicyclic, etc.), the aromatic rings of the aryl group may be joined at a single point (e.g., biphenyl), or fused (e.g., naphthyl). The aryl group may be optionally substituted by one or more substituents, e.g., 1 to 5 substituents, at any point of attachment. Exemplary substituents include, but are not limited to, —H, -halogen, —O—C_1-C_6 alkyl, C_1-C_6alkyl, —OC_1-C_6 alkenyl, —OC_1-C_6alkynyl, —C_1-C_6alkenyl, —C_1-C_6alkynyl, —OH, —OP(O)$(OH)_2$, —OC(O)C_1-C_6alkyl, —C(O)C_1-C_6alkyl, —OC(O)OC_1-C_6alkyl, NH_2, NH(C_1-C_6alkyl), N(C_1-C_6alkyl$)_2$, —S(O)$_2$—C_1-C_6alkyl, —S(O)NHC_1-C_6alkyl, and S(O)N(C_1-C_6 alkyl$)_2$. The substituents can themselves be optionally substituted. Furthermore when containing two fused rings the aryl groups herein defined may have an unsaturated or partially saturated ring fused with a fully saturated ring. Exemplary ring systems of these aryl groups include indanyl, indenyl, tetrahydronaphthalenyl, and tetrahydrobenzoannulenyl.

Unless otherwise specifically defined, "heteroaryl" means a monovalent monocyclic aromatic radical of 5 to 10 ring atoms or a polycyclic aromatic radical, containing one or more ring heteroatoms selected from N, O, or S, the remaining ring atoms being C. Heteroaryl as herein defined also means a bicyclic heteroaromatic group wherein the heteroatom is selected from N, O, or S. The aromatic radical is optionally substituted independently with one or more substituents described herein. Examples include, but are not limited to, furyl, thienyl, pyrrolyl, pyridyl, pyrazolyl, pyrimidinyl, imidazolyl, isoxazolyl, oxazolyl, oxadiazolyl, pyrazinyl, indolyl, thiophen-2-yl, quinolyl, benzopyranyl, isothiazolyl, thiazolyl, thiadiazole, indazole, benzimidazolyl, thieno[3,2-b]thiophene, triazolyl, triazinyl, imidazo[1,2-b]pyrazolyl, furo[2,3-c]pyridinyl, imidazo[1,2-a]pyridinyl, indazolyl, pyrrolo[2,3-c]pyridinyl, pyrrolo[3,2-c]pyridinyl, pyrazolo[3,4-c]pyridinyl, thieno[3,2-c]pyridinyl, thieno[2,3-c]pyridinyl, thieno[2,3-b]pyridinyl, benzothiazolyl, indolyl, indolinyl, indolinonyl, dihydrobenzothiophenyl, dihydrobenzofuranyl, benzofuran, chromanyl, thiochromanyl, tetrahydroquinolinyl, dihydrobenzothiazine, dihydrobenzoxanyl, quinolinyl, isoquinolinyl, 1,6-naphthyridinyl, benzo[de]isoquinolinyl, pyrido[4,3-b][1,6]naphthyridinyl, thieno[2,3-b]pyrazinyl, quinazolinyl, tetrazolo[1,5-a]pyridinyl, [1,2,4]triazolo[4,3-a]pyridinyl, isoindolyl, pyrrolo[2,3-b]pyridinyl, pyrrolo[3,4-b]pyridinyl, pyrrolo[3,2-b]pyridinyl, imidazo[5,4-b]pyridinyl, pyrrolo[1,2-a]pyrimidinyl, tetrahydro pyrrolo[1,2-a]pyrimidinyl, 3,4-dihydro-2H-1λ^2-pyrrolo[2,1-b]pyrimidine, dibenzo[b,d] thiophene, pyridin-2-one, furo[3,2-c]pyridinyl, furo[2,3-c]pyridinyl, 1H-pyrido[3,4-b][1,4] thiazinyl, benzooxazolyl, benzoisoxazolyl, furo[2,3-b]pyridinyl, benzothiophenyl, 1,5-naphthyridinyl, furo[3,2-b]pyridine, [1,2,4]triazolo[1,5-a]pyridinyl, benzo [1,2,3]triazolyl, imidazo[1,2-a]pyrimidinyl, [1,2,4]triazolo[4,3-b]pyridazinyl, benzo[c][1,2,5]thiadiazolyl, benzo[c][1,2,5]oxadiazole, 1,3-dihydro-2H-benzo[d]imidazol-2-one, 3,4-dihydro-2H-pyrazolo [1,5-b][1,2]oxazinyl, 4,5,6,7-tetrahydropyrazolo[1,5-a]pyridinyl, thiazolo[5,4-d]thiazolyl, imidazo[2,1-b][1,3,4]thiadiazolyl, thieno[2,3-b]pyrrolyl, 3H-indolyl, and derivatives thereof. Furthermore when containing two fused rings the aryl groups herein defined may have an unsaturated or partially saturated ring fused with a fully saturated ring. Exemplary ring systems of these heteroaryl groups include indolinyl, indolinonyl, dihydrobenzothiophenyl, dihydrobenzofuran, chromanyl, thiochromanyl, tetrahydroquinolinyl, dihydrobenzothiazine, and dihydrobenzoxanyl.

Halogen or "halo" refers to fluorine, chlorine, bromine, or iodine.

Alkyl refers to a straight or branched chain saturated hydrocarbon containing 1-12 carbon atoms. Examples of a C_1-C_6 alkyl group include, but are not limited to, methyl, ethyl, propyl, butyl, pentyl, hexyl, isopropyl, isobutyl, sec-butyl, tert-butyl, isopentyl, neopentyl, and isohexyl.

The term "haloalkyl" as used herein refers to an alkyl group, as defined herein, which is substituted one or more halogen. Examples of haloalkyl groups include, but are not limited to, trifluoromethyl, difluoromethyl, pentafluoroethyl, trichloromethyl, etc.

"Alkoxy" refers to a straight or branched chain saturated hydrocarbon containing 1-12 carbon atoms containing a terminal "0" in the chain. Examples of alkoxy groups include without limitation, methoxy, ethoxy, propoxy, butoxy, t-butoxy, or pentoxy groups.

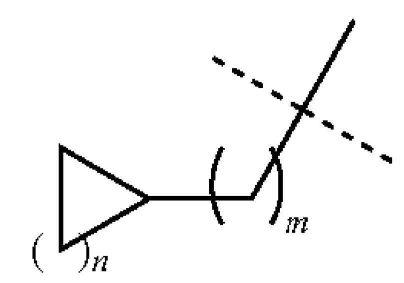
"Alkenyl" refers to a straight or branched chain unsaturated hydrocarbon containing 2-12 carbon atoms. The "alkenyl" group contains at least one double bond in the chain. Examples of alkenyl groups include ethenyl, propenyl, n-butenyl, iso-butenyl, pentenyl, or hexenyl.

"Alkynyl" refers to a straight or branched chain unsaturated hydrocarbon containing 2-12 carbon atoms. The "alkynyl" group contains at least one triple bond in the chain. Examples of alkenyl groups include ethynyl, propargyl, n-butynyl, iso-butynyl, pentynyl, or hexynyl.

"Cycloalkyl" means monocyclic saturated carbon rings containing 3-18 carbon atoms. Examples of cycloalkyl groups include, without limitations, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptanyl, cyclooctanyl, norboranyl, norborenyl, bicyclo[2.2.2]octanyl, or bicyclo[2.2.2]octenyl.

The term "haloCycloalkyl" as used herein refers to a cycloalkyl ring, as defined herein, which is substituted one or more halogen. Examples of halocycloalkyl groups include, but are not limited to, monochlorcyclopropyl, dichlorocyclobutyl, monocbromocyclopentyl, dichlorocyclohexyl, dibromocycloheptanyl, tribromocyclooctanyl, dichloronorboranyl, dichloronorborenyl, monochlorobicyclo[2.2.2]octanyl, or dibromobicyclo[2.2.2]octenyl, etc.

"Cycloalkylalkyl" means monocyclic saturated carbon rings containing 3-18 carbon atoms further substituted with C_1-C_6 alkyl groups. In general cycloalkylalkyl groups herein described display the following formula



where m is an integer from 1 to 6 and n is an integer from 1 to 16.

"Heterocyclyl" or "heterocycloalkyl" monocyclic rings containing carbon and heteroatoms taken from oxygen, nitrogen, or sulfur and wherein there is not delocalized π electrons (aromaticity) shared among the ring carbon or heteroatoms; heterocyclyl rings include, but are not limited to, oxetanyl, azetadinyl, tetrahydrofuranyl, pyrrolidinyl, oxazolinyl, oxazolidinyl, thiazolinyl, thiazolidinyl, pyranyl, thiopyranyl, tetrahydropyranyl, dioxalinyl, piperidinyl, morpholinyl, thiomorpholinyl, thiomorpholinyl S-oxide, thiomorpholinyl S-dioxide, piperazinyl, azepinyl, oxepinyl, diazepinyl, tropanyl, and homotropanyl. In accordance with the present invention, 3- to 8-membered heterocyclyl refers to saturated or partially saturated non aromatic rings structures containing between 3 and 8 atoms in which there is at least one heteroatoms selected from the group N, O, or S.

"Oxo" refers to the group (═O).

Thioxo refers to the group (═S).

The term "solvate" refers to a complex of variable stoichiometry formed by a solute and solvent. Such solvents for the purpose of the invention may not interfere with the biological activity of the solute. Examples of suitable solvents include, but are not limited to, water, MeOH, EtOH, and AcOH. Solvates wherein water is the solvent molecule are typically referred to as hydrates. Hydrates include compositions containing stoichiometric amounts of water, as well as compositions containing variable amounts of water.

The term "isomer" refers to compounds that have the same composition and molecular weight but differ in physical and/or chemical properties. The structural difference may be in constitution (geometric isomers) or in the ability to rotate the plane of polarized light (stereoisomers). With regard to stereoisomers, the compounds of Formula (I) may have one or more asymmetric carbon atom and may occur as racemates, racemic mixtures and as individual enantiomers or diastereomers.

The disclosure also includes pharmaceutical compositions comprising an effective amount of a disclosed compound and a pharmaceutically acceptable carrier. Representative "pharmaceutically acceptable salts" include, e.g., water-soluble and water-insoluble salts, such as the acetate, amsonate (4,4-diaminostilbene-2,2-disulfonate), benzenesulfonate, benzonate, bicarbonate, bisulfate, bitartrate, borate, bromide, butyrate, calcium, calcium edetate, camsylate, carbonate, chloride, citrate, clavulariate, dihydrochloride, edetate, edisylate, estolate, esylate, fiunarate, gluceptate, gluconate, glutamate, glycollylarsanilate, hexafluorophosphate, hexylresorcinate, hydrabamine, hydrobromide, hydrochloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, magnesium, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, N-methylglucamine ammonium salt, 3-hydroxy-2-naphthoate, oleate, oxalate, palmitate, pamoate (1,1-methene-bis-2-hydroxy-3-naphthoate, einbonate), pantothenate, phosphate/diphosphate, picrate, polygalacturonate, propionate, p-toluenesulfonate, salicylate, stearate, subacetate, succinate, sulfate, sulfosalicylate, suramate, tannate, tartrate, teoclate, tosylate, triethiodide, and valerate salts.

A "patient" or "subject" is a mammal, e.g., a human, mouse, rat, guinea pig, dog, cat, horse, cow, pig, or non-human primate, such as a monkey, chimpanzee, baboon or rhesus.

An "effective amount" when used in connection with a compound is an amount effective for treating or preventing a disease in a subject as described herein.

The term "carrier", as used in this disclosure, encompasses carriers, excipients, and diluents and means a material, composition or vehicle, such as a liquid or solid filler, diluent, excipient, solvent or encapsulating material, involved in carrying or transporting a pharmaceutical agent from one organ, or portion of the body, to another organ, or portion of the body of a subject.

The term "treating" with regard to a subject, refers to improving at least one symptom of the subject's disorder. Treating includes curing, improving, or at least partially ameliorating the disorder.

The term "disorder" is used in this disclosure to mean, and is used interchangeably with, the terms disease, condition, or illness, unless otherwise indicated.

The term "administer", "administering", or "administration" as used in this disclosure refers to either directly administering a disclosed compound or pharmaceutically acceptable salt of the disclosed compound or a composition to a subject, or administering a prodrug derivative or analog of the compound or pharmaceutically acceptable salt of the compound or composition to the subject, which can form an equivalent amount of active compound within the subject's body.

The term "prodrug," as used in this disclosure, means a compound which is convertible in vivo by metabolic means (e.g., by hydrolysis) to a disclosed compound.

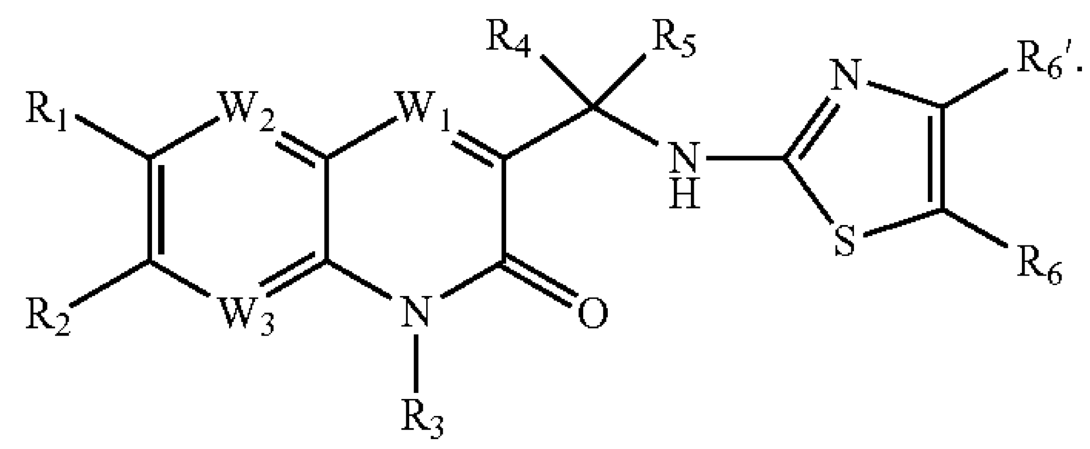
In one embodiment of the compounds of Formula I, two adjacent R_6 and/or $R_{6'}$ combine to form pyrrolidinyl, piperidinyl, phenyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, pyrrolyl, pyrazolyl, oxadiazolyl, thiadiazolyl, furyl, imidazolyl, pyridyl, pyrimidinyl, pyrrolyl, furyl, thienyl, oxazolyl, thiazolyl, isoxazolyl, isothiazolyl, imidazolyl, pyrazolyl, oxadiazolyl, thiadiazolyl, triazolyl, tetrazolyl, pyrazinyl, pyridazinyl, triazinyl, pyridinyl, pyrimidinyl, morpholinyl, thiomorpholinyl, oxazolonyl, oxazinonyl, dihydrooxazinonyl, imidazolonyl, pyrrolonyl, thiazolonyl, dihydropyridinonyl, dihydrothiazinedioxide, dihydrodioxinyl, dihydropyranonyl, dihydrothiophenedioxide, piperidinonyl, pyrrolidinonyl, or dihydrooxazinonyl.

In another embodiment of the compounds of Formula I, R_6 is CN, $C(O)NH_2$, or —$NHCOR_7$.

In some embodiments of the compounds of Formula I, R_6' is methyl, ethyl, isopropyl, phenyl, pyridinyl, or isobutyl.

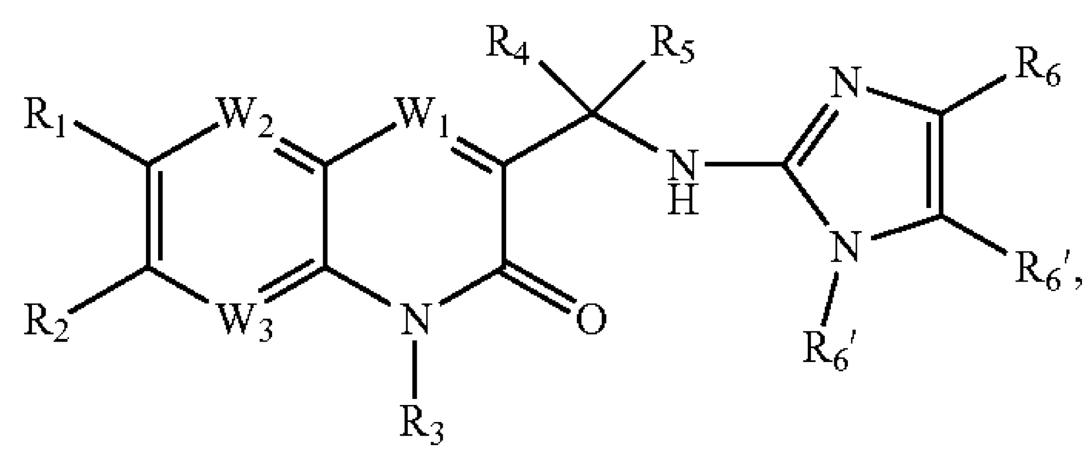
In another embodiment, the compounds of Formula have the Formula Ia:

Ia



In another embodiment, the compounds of Formula have the Formula Ib:

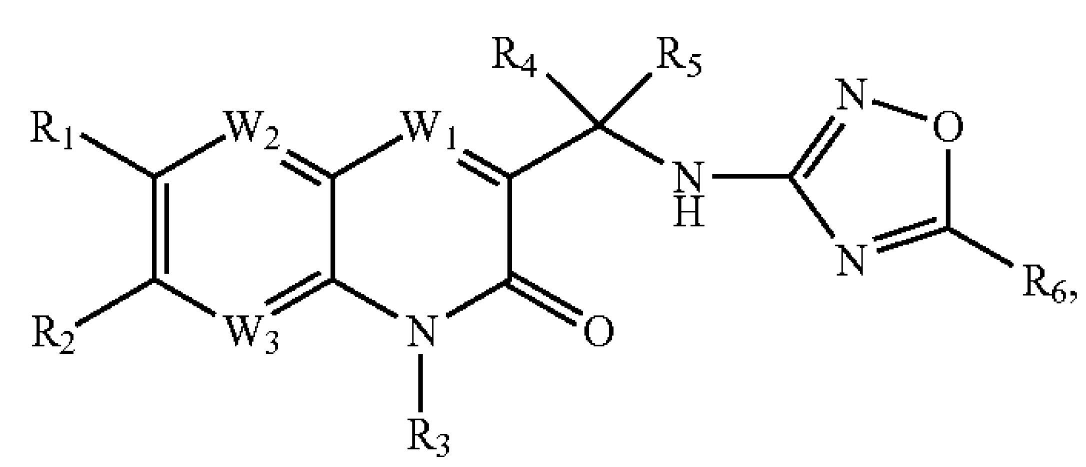
Ib



wherein the two adjacent $R_{6'}$, or the two adjacent R_6 and $R_{6'}$ can combine to form a 5- to 7-membered heterocyclyl ring.

In another embodiment, the compounds of Formula have the Formula Ic:

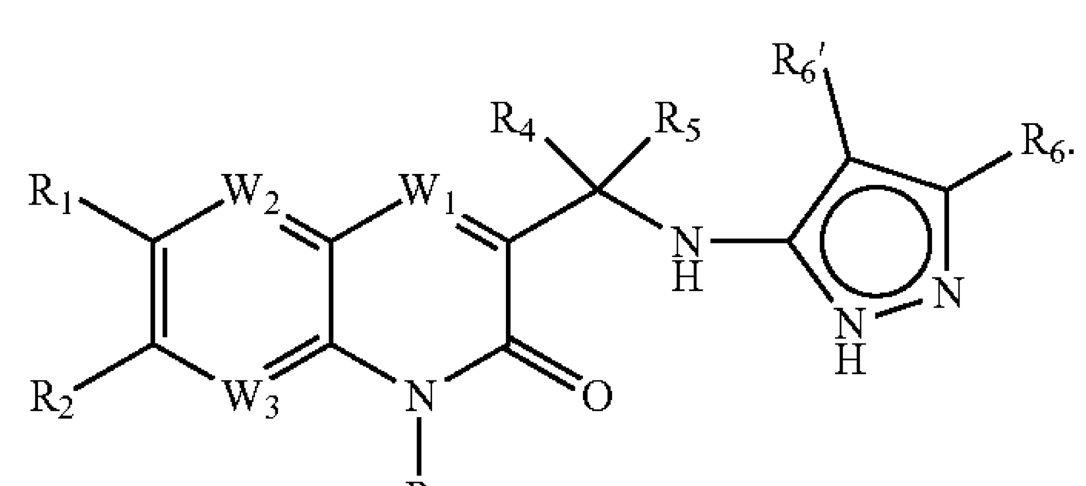
Ic



wherein R_6 is CN, $R_7NHC(O)$— or $R_7S(O)_2$—.

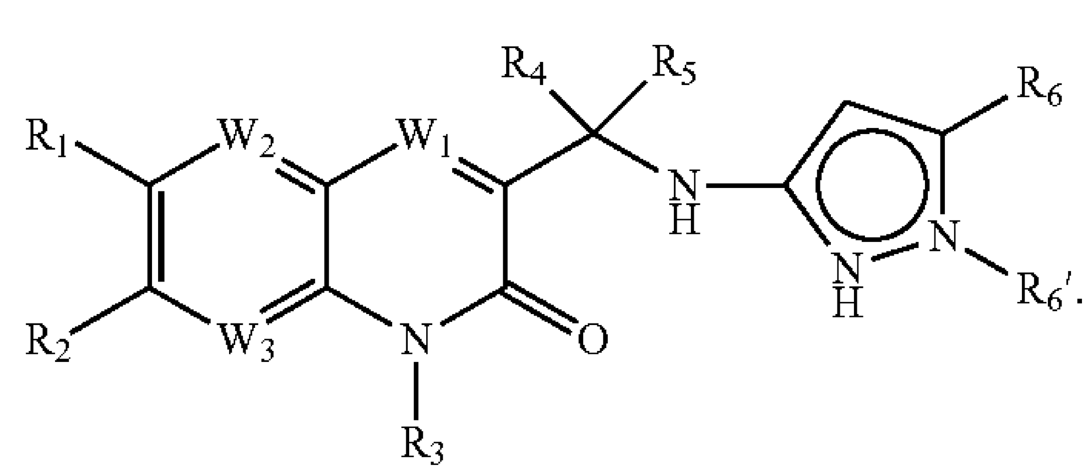
In another embodiment, the compounds of Formula have the Formula Id:

Id



In another embodiment, the compounds of Formula have the Formula Ie:

Ie



In another embodiment of compounds of Formula (I), R_4 and R_5 are H.

In yet another embodiment of compounds of Formula (I), R_4 is H and R_5 is methyl.

In another embodiment, R_4 is H and R_5 is (S)-methyl.

In further embodiments, R_4 and R_5 are halogen.

In some embodiments, R_4 is F and R_5 is methyl.

Other embodiments relate to compounds of Formula (I) where R_4 and R_5 can combine to form a C_3-C_5 cycloalkyl.

Other embodiments relate to compounds of Formula (I) where R_6 is CN, $CONH_2$, or $NHCOR_7$, and R_6' is H, methyl, or ethyl.

In one embodiment of the compounds of Formula (I), W_1, W_2, and W_3 are independently CH.

In another embodiment, W_1, W_2, or W_3 is N.

In another embodiment, W_3 is CF.

In another embodiment, R_1 can be halogen. In another embodiment, R_1 is chloro.

In one embodiment, R_2 can be H or C_1-C_6 alkoxy. In another embodiment, R_2 is C_1-C_6 alkoxy substituted with heteroaryl or 3- to 8-membered heterocyclyl.

In one embodiment, illustrative compounds of the invention include:

2-{[(1S)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1,3-thiazole-5-carbonitrile,
2-{[1-(6-chloro-7-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1,3-thiazole-5-carbonitrile,
2-({1-[6-chloro-2-oxo-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-3-yl]ethyl}amino)-1,3-thiazole-5-carbonitrile,
2-{[(1S)-1-[6-chloro-2-oxo-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-3-yl]ethyl]amino}-1,3-thiazole-5-carbonitrile,
2-{[(1R)-1-[6-chloro-2-oxo-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-3-yl]ethyl]amino}-1,3-thiazole-5-carbonitrile,
2-{[1-(6-chloro-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl)ethyl]amino}-1,3-thiazole-5-carbonitrile,
2-{[(1S)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-4-methyl-1,3-thiazole-5-carbonitrile,
N-(2-{[(1S)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1,3-thiazol-5-yl)acetamide,
ethyl 2-{[(1S)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-4-methyl-1,3-thiazole-5-carboxylate,
2-{[(1S)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1,3-thiazole-5-carboxamide,
2-{[(1S)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-4-methyl-1,3-thiazole-5-carboxamide,
6-chloro-3-[(1S)-1-{[5-(2-oxo-1,3-oxazolidin-3-yl)-1,2,4-thiadiazol-3-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
6-chloro-3-({[4-(pyridin-2-yl)-1,3-thiazol-2-yl]amino}methyl)-1,2-dihydroquinolin-2-one,
6-chloro-3-({[4-(3,4-difluorophenyl)-1,3-thiazol-2-yl]amino}methyl)-1,2-dihydroquinolin-2-one,
3-{[(1,3-benzothiazol-2-yl)amino]methyl}-6-methoxy-1,2-dihydroquinolin-2-one,
2-{[(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)methyl]amino}-4-ethyl-5-methylthiophene-3-carbonitrile, and
3-{[(dimethyl-1,3-thiazol-2-yl)amino]methyl}-6-methoxy-1,2-dihydroquinolin-2-one.

In another embodiment, non-limiting illustrative compounds of the invention include:

2-{[1-(6-chloro-7-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1,3-thiazole-5-carbonitrile,
2-{[1-(6-chloro-7-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-4-methyl-1,3-thiazole-5-carbonitrile,
2-{[1-(6-chloro-7-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-4-methoxy-1,3-thiazole-5-carbonitrile,
6-chloro-7-fluoro-3-(1-{[5-(2-oxo-1,3-oxazolidin-3-yl)-1,3-thiazol-2-yl]amino}ethyl)-1,2-dihydroquinolin-2-one,

methyl N-(2-{[1-(6-chloro-7-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1,3-thiazol-5-yl)carbamate,

2-{[1-(6-chloro-7-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-4-methyl-1,3-thiazole-5-carboxamide,

6-chloro-7-fluoro-3-(1-{[5-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl)-1,2-dihydroquinolin-2-one,

6-chloro-7-fluoro-3-(1-{[5-(5-methyl-1H-1,2,3-triazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl)-1,2-dihydroquinolin-2-one,

6-chloro-3-(1-{[5-(5-cyclopropyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl)-7-fluoro-1,2-dihydroquinolin-2-one,

6-chloro-3-(1-{[5-(5-cyclopropyl-1H-1,2,3-triazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl)-7-fluoro-1,2-dihydroquinolin-2-one,

6-chloro-7-fluoro-3-(1-{[4-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl)-1,2-dihydroquinolin-2-one,

6-chloro-7-fluoro-3-(1-{[4-(5-methyl-1H-1,2,3-triazol-1-yl)-1,3-oxazol-2-yl]amino}ethyl)-1,2-dihydroquinolin-2-one,

6-chloro-7-fluoro-3-(1-{[4-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-oxazol-2-yl]amino}ethyl)-1,2-dihydroquinolin-2-one,

6-chloro-7-fluoro-3-(1-{[4-(pyridin-3-yl)-1,3-thiazol-2-yl]amino}ethyl)-1,2-dihydroquinolin-2-one,

6-chloro-7-fluoro-3-(1-{[4-(pyridin-3-yl)-1,3-oxazol-2-yl]amino}ethyl)-1,2-dihydroquinolin-2-one,

3-{[1-(6-chloro-7-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1-methyl-1H-1,2,4-triazole-5-carboxamide,

6-chloro-3-(1-{[5-(1-cyclopropyl-1H-imidazol-5-yl)-1,3-thiazol-2-yl]amino}ethyl)-7-fluoro-1,2-dihydroquinolin-2-one,

6-chloro-3-[1-({5-[1-(cyclopropylmethyl)-1H-imidazol-5-yl]-1,3-thiazol-2-yl}amino)ethyl]-7-fluoro-1,2-dihydroquinolin-2-one,

3-{[1-(6-chloro-7-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1-methyl-1H-pyrazole-5-carboxamide,

2-{[1-(6-chloro-7-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1H-imidazole-5-carboxamide,

N-(2-{[1-(6-chloro-7-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1,3-oxazol-4-yl)acetamide,

2-{[(1S)-1-(6-chloro-7-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1,3-thiazole-5-carbonitrile,

2-{[(1S)-1-(6-chloro-7-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-4-methyl-1,3-thiazole-5-carbonitrile,

2-{[(1S)-1-(6-chloro-7-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-4-methoxy-1,3-thiazole-5-carbonitrile,

6-chloro-7-fluoro-3-[(1S)-1-{[5-(2-oxo-1,3-oxazolidin-3-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

methyl N-(2-{[(1S)-1-(6-chloro-7-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1,3-thiazol-5-yl)carbamate,

2-{[(1S)-1-(6-chloro-7-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-4-methyl-1,3-thiazole-5-carboxamide,

6-chloro-7-fluoro-3-[(1S)-1-{[5-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-7-fluoro-3-[(1S)-1-{[5-(5-methyl-1H-1,2,3-triazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1S)-1-{[5-(5-cyclopropyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-7-fluoro-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1S)-1-{[5-(5-cyclopropyl-1H-1,2,3-triazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-7-fluoro-1,2-dihydroquinolin-2-one,

6-chloro-7-fluoro-3-[(1S)-1-{[4-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-7-fluoro-3-[(1S)-1-{[4-(5-methyl-1H-1,2,3-triazol-1-yl)-1,3-oxazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-7-fluoro-3-[(1S)-1-{[4-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-oxazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-7-fluoro-3-[(1S)-1-{[4-(pyridin-3-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-7-fluoro-3-[(1S)-1-{[4-(pyridin-3-yl)-1,3-oxazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

3-{[(1S)-1-(6-chloro-7-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1-methyl-1H-1,2,4-triazole-5-carboxamide,

6-chloro-3-[(1S)-1-{[5-(1-cyclopropyl-1H-imidazol-5-yl)-1,3-thiazol-2-yl]amino}ethyl]-7-fluoro-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1S)-1-({5-[1-(cyclopropylmethyl)-1H-imidazol-5-yl]-1,3-thiazol-2-yl}amino)ethyl]-7-fluoro-1,2-dihydroquinolin-2-one,

3-{[(1S)-1-(6-chloro-7-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1-methyl-1H-pyrazole-5-carboxamide,

2-{[(1S)-1-(6-chloro-7-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1H-imidazole-5-carboxamide,

N-(2-{[(1S)-1-(6-chloro-7-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1,3-oxazol-4-yl)acetamide,

2-{[(1R)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1,3-thiazole-5-carbonitrile,

2-{[(1R)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-4-methyl-1,3-thiazole-5-carbonitrile,

2-{[(1R)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-4-methoxy-1,3-thiazole-5-carbonitrile,

6-chloro-3-[(1R)-1-{[5-(2-oxo-1,3-oxazolidin-3-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

methyl N-(2-{[(1R)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1,3-thiazol-5-yl)carbamate,

2-{[(1R)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-4-methyl-1,3-thiazole-5-carboxamide,

6-chloro-3-[(1R)-1-{[5-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1R)-1-{[5-(5-methyl-1H-1,2,3-triazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1R)-1-{[5-(5-cyclopropyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1R)-1-{[5-(5-cyclopropyl-1H-1,2,3-triazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1R)-1-{[4-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1R)-1-{[4-(5-methyl-1H-1,2,3-triazol-1-yl)-1,3-oxazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1R)-1-{[4-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-oxazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1R)-1-{[4-(pyridin-3-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
6-chloro-3-[(1R)-1-{[4-(pyridin-3-yl)-1,3-oxazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
3-{[(1R)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1-methyl-1H-1,2,4-triazole-5-carboxamide,
6-chloro-3-[(1R)-1-{[5-(1-cyclopropyl-1H-imidazol-5-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
6-chloro-3-[(1R)-1-({5-[1-(cyclopropylmethyl)-1H-imidazol-5-yl]-1,3-thiazol-2-yl}amino)ethyl]-1,2-dihydroquinolin-2-one,
3-{[(1R)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1-methyl-1H-pyrazole-5-carboxamide,
2-{[(1R)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1H-imidazole-5-carboxamide,
N-(2-{[(1R)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1,3-oxazol-4-yl)acetamide,
2-{[(1S)-1-(6-chloro-7-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1,3-thiazole-5-carbonitrile,
2-{[(1S)-1-(6-chloro-7-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-4-methyl-1,3-thiazole-5-carbonitrile,
2-{[(1S)-1-(6-chloro-7-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-4-methoxy-1,3-thiazole-5-carbonitrile,
6-chloro-7-methoxy-3-[(1S)-1-{[5-(2-oxo-1,3-oxazolidin-3-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
methyl N-(2-{[(1S)-1-(6-chloro-7-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1,3-thiazol-5-yl)carbamate,
2-{[(1S)-1-(6-chloro-7-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-4-methyl-1,3-thiazole-5-carboxamide,
6-chloro-7-methoxy-3-[(1S)-1-{[5-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
6-chloro-7-methoxy-3-[(1S)-1-{[5-(5-methyl-1H-1,2,3-triazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
6-chloro-3-[(1S)-1-{[5-(5-cyclopropyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-7-methoxy-1,2-dihydroquinolin-2-one,
6-chloro-3-[(1S)-1-{[5-(5-cyclopropyl-1H-1,2,3-triazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-7-methoxy-1,2-dihydroquinolin-2-one,
6-chloro-7-methoxy-3-[(1S)-1-{[4-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
6-chloro-7-methoxy-3-[(1S)-1-{[4-(5-methyl-1H-1,2,3-triazol-1-yl)-1,3-oxazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
6-chloro-7-methoxy-3-[(1S)-1-{[4-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-oxazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
6-chloro-7-methoxy-3-[(1S)-1-{[4-(pyridin-3-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
6-chloro-7-methoxy-3-[(1S)-1-{[4-(pyridin-3-yl)-1,3-oxazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
3-{[(1S)-1-(6-chloro-7-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1-methyl-1H-1,2,4-triazole-5-carboxamide,
6-chloro-3-[(1S)-1-{[5-(1-cyclopropyl-1H-imidazol-5-yl)-1,3-thiazol-2-yl]amino}ethyl]-7-methoxy-1,2-dihydroquinolin-2-one,
6-chloro-3-[(1S)-1-({5-[1-(cyclopropylmethyl)-1H-imidazol-5-yl]-1,3-thiazol-2-yl}amino)ethyl]-7-methoxy-1,2-dihydroquinolin-2-one,
3-{[(1S)-1-(6-chloro-7-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1-methyl-1H-pyrazole-5-carboxamide,
2-{[(1S)-1-(6-chloro-7-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1H-imidazole-5-carboxamide,
N-(2-{[(1S)-1-(6-chloro-7-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1,3-oxazol-4-yl)acetamide,
2-({1-[6-chloro-2-oxo-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-3-yl]ethyl}amino)-4-methyl-1,3-thiazole-5-carbonitrile,
2-({1-[6-chloro-2-oxo-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-3-yl]ethyl}amino)-4-methoxy-1,3-thiazole-5-carbonitrile,
6-chloro-3-(1-{[5-(2-oxo-1,3-oxazolidin-3-yl)-1,3-thiazol-2-yl]amino}ethyl)-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-2-one,
methyl N-[2-({1-[6-chloro-2-oxo-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-3-yl]ethyl}amino)-1,3-thiazol-5-yl]carbamate,
2-({1-[6-chloro-2-oxo-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-3-yl]ethyl}amino)-4-methyl-1,3-thiazole-5-carboxamide,
6-chloro-3-(1-{[5-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl)-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-2-one,
6-chloro-3-(1-{[5-(5-methyl-1H-1,2,3-triazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl)-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-2-one,
6-chloro-3-(1-{[5-(5-cyclopropyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl)-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-2-one,
6-chloro-3-(1-{[5-(5-cyclopropyl-1H-1,2,3-triazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl)-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-2-one,
6-chloro-3-(1-{[4-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl)-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-2-one,
6-chloro-3-(1-{[4-(5-methyl-1H-1,2,3-triazol-1-yl)-1,3-oxazol-2-yl]amino}ethyl)-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-2-one,
6-chloro-3-(1-{[4-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-oxazol-2-yl]amino}ethyl)-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-2-one,
6-chloro-7-(pyridin-2-ylmethoxy)-3-(1-{[4-(pyridin-3-yl)-1,3-thiazol-2-yl]amino}ethyl)-1,2-dihydroquinolin-2-one,
6-chloro-7-(pyridin-2-ylmethoxy)-3-(1-{[4-(pyridin-3-yl)-1,3-oxazol-2-yl]amino}ethyl)-1,2-dihydroquinolin-2-one,
3-({1-[6-chloro-2-oxo-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-3-yl]ethyl}amino)-1-methyl-1H-1,2,4-triazole-5-carboxamide,
6-chloro-3-(1-{[5-(1-cyclopropyl-1H-imidazol-5-yl)-1,3-thiazol-2-yl]amino}ethyl)-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-2-one,
6-chloro-3-[1-({5-[1-(cyclopropylmethyl)-1H-imidazol-5-yl]-1,3-thiazol-2-yl}amino)ethyl]-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-2-one,
3-({1-[6-chloro-2-oxo-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-3-yl]ethyl}amino)-1-methyl-1H-pyrazole-5-carboxamide,
2-({1-[6-chloro-2-oxo-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-3-yl]ethyl}amino)-1H-imidazole-5-carboxamide,

N-[2-({1-[6-chloro-2-oxo-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-3-yl]ethyl}amino)-1,3-oxazol-4-yl]acetamide,

2-{[(1S)-1-[6-chloro-2-oxo-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-3-yl]ethyl]amino}-4-methyl-1,3-thiazole-5-carbonitrile,

2-{[(1S)-1-[6-chloro-2-oxo-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-3-yl]ethyl]amino}-4-methoxy-1,3-thiazole-5-carbonitrile,

6-chloro-3-[(1S)-1-{[5-(2-oxo-1,3-oxazolidin-3-yl)-1,3-thiazol-2-yl]amino}ethyl]-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-2-one,

methyl N-(2-{[(1S)-1-[6-chloro-2-oxo-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-3-yl]ethyl]amino}-1,3-thiazol-5-yl)carbamate,

2-{[(1S)-1-[6-chloro-2-oxo-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-3-yl]ethyl]amino}-4-methyl-1,3-thiazole-5-carboxamide,

6-chloro-3-[(1S)-1-{[5-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1S)-1-{[5-(5-methyl-1H-1,2,3-triazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1S)-1-{[5-(5-cyclopropyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1S)-1-{[5-(5-cyclopropyl-1H-1,2,3-triazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1S)-1-{[4-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1S)-1-{[4-(5-methyl-1H-1,2,3-triazol-1-yl)-1,3-oxazol-2-yl]amino}ethyl]-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1S)-1-{[4-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-oxazol-2-yl]amino}ethyl]-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-2-one,

6-chloro-7-(pyridin-2-ylmethoxy)-3-[(1S)-1-{[4-(pyridin-3-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-7-(pyridin-2-ylmethoxy)-3-[(1S)-1-{[4-(pyridin-3-yl)-1,3-oxazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

3-{[(1S)-1-[6-chloro-2-oxo-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-3-yl]ethyl]amino}-1-methyl-1H-1,2,4-triazole-5-carboxamide,

6-chloro-3-[(1S)-1-{[5-(1-cyclopropyl-1H-imidazol-5-yl)-1,3-thiazol-2-yl]amino}ethyl]-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1S)-1-({5-[1-(cyclopropylmethyl)-1H-imidazol-5-yl]-1,3-thiazol-2-yl}amino)ethyl]-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-2-one,

3-{[(1S)-1-[6-chloro-2-oxo-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-3-yl]ethyl]amino}-1-methyl-1H-pyrazole-5-carboxamide,

2-{[(1S)-1-[6-chloro-2-oxo-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-3-yl]ethyl]amino}-1H-imidazole-5-carboxamide,

N-(2-{[(1S)-1-[6-chloro-2-oxo-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-3-yl]ethyl]amino}-1,3-oxazol-4-yl)acetamide,

2-{[(1S)-1-{6-chloro-2-oxo-7-[(1R)-1-(pyridin-2-yl)ethoxy]-1,2-dihydroquinolin-3-yl}ethyl]amino}-1,3-thiazole-5-carbonitrile,

2-{[(1S)-1-{6-chloro-2-oxo-7-[(1R)-1-(pyridin-2-yl)ethoxy]-1,2-dihydroquinolin-3-yl}ethyl]amino}-4-methyl-1,3-thiazole-5-carbonitrile,

2-{[(1S)-1-{6-chloro-2-oxo-7-[(1R)-1-(pyridin-2-yl)ethoxy]-1,2-dihydroquinolin-3-yl}ethyl]amino}-4-methoxy-1,3-thiazole-5-carbonitrile,

6-chloro-3-[(1S)-1-{[5-(2-oxo-1,3-oxazolidin-3-yl)-1,3-thiazol-2-yl]amino}ethyl]-7-[(1R)-1-(pyridin-2-yl)ethoxy]-1,2-dihydroquinolin-2-one,

methyl N-(2-{[(1S)-1-{6-chloro-2-oxo-7-[(1R)-1-(pyridin-2-yl)ethoxy]-1,2-dihydroquinolin-3-yl}ethyl]amino}-1,3-thiazol-5-yl)carbamate,

2-{[(1S)-1-{6-chloro-2-oxo-7-[(1R)-1-(pyridin-2-yl)ethoxy]-1,2-dihydroquinolin-3-yl}ethyl]amino}-4-methyl-1,3-thiazole-5-carboxamide,

6-chloro-3-[(1S)-1-{[5-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-7-[(1R)-1-(pyridin-2-yl)ethoxy]-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1S)-1-{[5-(5-methyl-1H-1,2,3-triazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-7-[(1R)-1-(pyridin-2-yl)ethoxy]-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1S)-1-{[5-(5-cyclopropyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-[(1R)-1-(pyridin-2-yl)ethoxy]-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1S)-1-{[5-(5-cyclopropyl-1H-1,2,3-triazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-[(1R)-1-(pyridin-2-yl)ethoxy]-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1S)-1-{[4-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-7-[(1R)-1-(pyridin-2-yl)ethoxy]-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1S)-1-{[4-(5-methyl-1H-1,2,3-triazol-1-yl)-1,3-oxazol-2-yl]amino}ethyl]-7-[(1R)-1-(pyridin-2-yl)ethoxy]-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1S)-1-{[4-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-oxazol-2-yl]amino}ethyl]-7-[(1R)-1-(pyridin-2-yl)ethoxy]-1,2-dihydroquinolin-2-one,

6-chloro-7-[(1R)-1-(pyridin-2-yl)ethoxy]-3-[(1S)-1-{[4-(pyridin-3-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-7-[(1R)-1-(pyridin-2-yl)ethoxy]-3-[(1S)-1-{[4-(pyridin-3-yl)-1,3-oxazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

3-{[(1S)-1-{6-chloro-2-oxo-7-[(1R)-1-(pyridin-2-yl)ethoxy]-1,2-dihydroquinolin-3-yl}ethyl]amino}-1-methyl-1H-1,2,4-triazole-5-carboxamide,

6-chloro-3-[(1S)-1-{[5-(1-cyclopropyl-1H-imidazol-5-yl)-1,3-thiazol-2-yl]amino}ethyl]-7-[(1R)-1-(pyridin-2-yl)ethoxy]-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1S)-1-({5-[1-(cyclopropylmethyl)-1H-imidazol-5-yl]-1,3-thiazol-2-yl}amino)ethyl]-[(1R)-1-(pyridin-2-yl)ethoxy]-1,2-dihydroquinolin-2-one,

3-{[(1S)-1-{6-chloro-2-oxo-7-[(1R)-1-(pyridin-2-yl)ethoxy]-1,2-dihydroquinolin-3-yl}ethyl]amino}-1-methyl-1H-pyrazole-5-carboxamide,

2-{[(1S)-1-{6-chloro-2-oxo-7-[(1R)-1-(pyridin-2-yl)ethoxy]-1,2-dihydroquinolin-3-yl}ethyl]amino}-1H-imidazole-5-carboxamide,

N-(2-{[(1S)-1-{6-chloro-2-oxo-7-[(1R)-1-(pyridin-2-yl)ethoxy]-1,2-dihydroquinolin-3-yl}ethyl]amino}-1,3-oxazol-4-yl)acetamide,

2-{[(1S)-1-[6-chloro-7-(cyclopropylmethoxy)-2-oxo-1,2-dihydroquinolin-3-yl]ethyl]amino}-1,3-thiazole-5-carbonitrile,

2-{[(1S)-1-[6-chloro-7-(cyclopropylmethoxy)-2-oxo-1,2-dihydroquinolin-3-yl]ethyl]amino}-4-methyl-1,3-thiazole-5-carbonitrile, 2-{[(1S)-1-[6-chloro-7-(cyclopropylmethoxy)-2-oxo-1,2-dihydroquinolin-3-yl]ethyl]amino}-4-methoxy-1,3-thiazole-5-carbonitrile,

6-chloro-7-(cyclopropylmethoxy)-3-[(1S)-1-{[5-(2-oxo-1,3-oxazolidin-3-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

methyl N-(2-{[(1S)-1-[6-chloro-7-(cyclopropylmethoxy)-2-oxo-1,2-dihydroquinolin-3-yl]ethyl]amino}-1,3-thiazol-5-yl)carbamate,

2-{[(1S)-1-[6-chloro-7-(cyclopropylmethoxy)-2-oxo-1,2-dihydroquinolin-3-yl]ethyl]amino}-4-methyl-1,3-thiazole-5-carboxamide,

6-chloro-7-(cyclopropylmethoxy)-3-[(1S)-1-{[5-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-7-(cyclopropylmethoxy)-3-[(1S)-1-{[5-(5-methyl-1H-1,2,3-triazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1S)-1-{[5-(5-cyclopropyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-7-(cyclopropylmethoxy)-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1S)-1-{[5-(5-cyclopropyl-1H-1,2,3-triazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-7-(cyclopropylmethoxy)-1,2-dihydroquinolin-2-one,

6-chloro-7-(cyclopropylmethoxy)-3-[(1S)-1-{[4-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-7-(cyclopropylmethoxy)-3-[(1S)-1-{[4-(5-methyl-1H-1,2,3-triazol-1-yl)-1,3-oxazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-7-(cyclopropylmethoxy)-3-[(1S)-1-{[4-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-oxazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-7-(cyclopropylmethoxy)-3-[(1S)-1-{[4-(pyridin-3-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-7-(cyclopropylmethoxy)-3-[(1S)-1-{[4-(pyridin-3-yl)-1,3-oxazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

3-{[(1S)-1-[6-chloro-7-(cyclopropylmethoxy)-2-oxo-1,2-dihydroquinolin-3-yl]ethyl]amino}-1-methyl-1H-1,2,4-triazole-5-carboxamide,

6-chloro-3-[(1S)-1-{[5-(1-cyclopropyl-1H-imidazol-5-yl)-1,3-thiazol-2-yl]amino}ethyl]-7-(cyclopropylmethoxy)-1,2-dihydroquinolin-2-one,

6-chloro-7-(cyclopropylmethoxy)-3-[(1S)-1-({5-[1-(cyclopropylmethyl)-1H-imidazol-5-yl]-1,3-thiazol-2-yl}amino)ethyl]-1,2-dihydroquinolin-2-one,

3-{[(1S)-1-[6-chloro-7-(cyclopropylmethoxy)-2-oxo-1,2-dihydroquinolin-3-yl]ethyl]amino}-1-methyl-1H-pyrazole-5-carboxamide,

2-{[(1S)-1-[6-chloro-7-(cyclopropylmethoxy)-2-oxo-1,2-dihydroquinolin-3-yl]ethyl]amino}-1H-imidazole-5-carboxamide,

N-(2-{[(1S)-1-[6-chloro-7-(cyclopropylmethoxy)-2-oxo-1,2-dihydroquinolin-3-yl]ethyl]amino}-1,3-oxazol-4-yl)acetamide,

2-{[(1S)-1-(6-chloro-8-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1,3-thiazole-5-carbonitrile,

2-{[(1S)-1-(6-chloro-8-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-4-methyl-1,3-thiazole-5-carbonitrile,

2-{[(1S)-1-(6-chloro-8-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-4-methoxy-1,3-thiazole-5-carbonitrile,

6-chloro-8-fluoro-3-[(1S)-1-{[5-(2-oxo-1,3-oxazolidin-3-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

methyl N-(2-{[(1S)-1-(6-chloro-8-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1,3-thiazol-5-yl)carbamate,

2-{[(1S)-1-(6-chloro-8-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-4-methyl-1,3-thiazole-5-carboxamide,

6-chloro-8-fluoro-3-[(1S)-1-{[5-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-8-fluoro-3-[(1S)-1-{[5-(5-methyl-1H-1,2,3-triazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1S)-1-{[5-(5-cyclopropyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-8-fluoro-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1S)-1-{[5-(5-cyclopropyl-1H-1,2,3-triazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-8-fluoro-1,2-dihydroquinolin-2-one,

6-chloro-8-fluoro-3-[(1S)-1-{[4-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-8-fluoro-3-[(1S)-1-{[4-(5-methyl-1H-1,2,3-triazol-1-yl)-1,3-oxazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-8-fluoro-3-[(1S)-1-{[4-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-oxazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-8-fluoro-3-[(1S)-1-{[4-(pyridin-3-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-8-fluoro-3-[(1S)-1-{[4-(pyridin-3-yl)-1,3-oxazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

3-{[(1S)-1-(6-chloro-8-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1-methyl-1H-1,2,4-triazole-5-carboxamide,

6-chloro-3-[(1S)-1-{[5-(1-cyclopropyl-1H-imidazol-5-yl)-1,3-thiazol-2-yl]amino}ethyl]-8-fluoro-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1S)-1-({5-[1-(cyclopropylmethyl)-1H-imidazol-5-yl]-1,3-thiazol-2-yl}amino)ethyl]-8-fluoro-1,2-dihydroquinolin-2-one,

3-{[(1S)-1-(6-chloro-8-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1-methyl-1H-pyrazole-5-carboxamide,

2-{[(1S)-1-(6-chloro-8-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1H-imidazole-5-carboxamide,

N-(2-{[(1S)-1-(6-chloro-8-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1,3-oxazol-4-yl)acetamide,

2-{[(1S)-1-[6-chloro-2-oxo-7-(propan-2-yloxy)-1,2-dihydroquinolin-3-yl]ethyl]amino}-1,3-thiazole-5-carbonitrile,

2-{[(1S)-1-[6-chloro-2-oxo-7-(propan-2-yloxy)-1,2-dihydroquinolin-3-yl]ethyl]amino}-4-methyl-1,3-thiazole-5-carbonitrile,

2-{[(1S)-1-[6-chloro-2-oxo-7-(propan-2-yloxy)-1,2-dihydroquinolin-3-yl]ethyl]amino}-4-methoxy-1,3-thiazole-5-carbonitrile,

6-chloro-3-[(1S)-1-{[5-(2-oxo-1,3-oxazolidin-3-yl)-1,3-thiazol-2-yl]amino}ethyl]-7-(propan-2-yloxy)-1,2-dihydroquinolin-2-one,

methyl N-(2-{[(1S)-1-[6-chloro-2-oxo-7-(propan-2-yloxy)-1,2-dihydroquinolin-3-yl]ethyl]amino}-1,3-thiazol-5-yl) carbamate,

2-{[(1S)-1-[6-chloro-2-oxo-7-(propan-2-yloxy)-1,2-dihydroquinolin-3-yl]ethyl]amino}-4-methyl-1,3-thiazole-5-carboxamide,

6-chloro-3-[(1S)-1-{[5-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-7-(propan-2-yloxy)-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1S)-1-{[5-(5-methyl-1H-1,2,3-triazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-7-(propan-2-yloxy)-1,2-dihydroquinolin-2-one,
6-chloro-3-[(1S)-1-{[5-(5-cyclopropyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-7-(propan-2-yloxy)-1,2-dihydroquinolin-2-one,
6-chloro-3-[(1S)-1-{[5-(5-cyclopropyl-1H-1,2,3-triazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-7-(propan-2-yloxy)-1,2-dihydroquinolin-2-one,
6-chloro-3-[(1S)-1-{[4-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-7-(propan-2-yloxy)-1,2-dihydroquinolin-2-one,
6-chloro-3-[(1S)-1-{[4-(5-methyl-1H-1,2,3-triazol-1-yl)-1,3-oxazol-2-yl]amino}ethyl]-7-(propan-2-yloxy)-1,2-dihydroquinolin-2-one,
6-chloro-3-[(1S)-1-{[4-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-oxazol-2-yl]amino}ethyl]-7-(propan-2-yloxy)-1,2-dihydroquinolin-2-one,
6-chloro-7-(propan-2-yloxy)-3-[(1S)-1-{[4-(pyridin-3-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
6-chloro-7-(propan-2-yloxy)-3-[(1S)-1-{[4-(pyridin-3-yl)-1,3-oxazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
3-{[(1S)-1-[6-chloro-2-oxo-7-(propan-2-yloxy)-1,2-dihydroquinolin-3-yl]ethyl]amino}-1-methyl-1H-1,2,4-triazole-5-carboxamide,
6-chloro-3-[(1S)-1-{[5-(1-cyclopropyl-1H-imidazol-5-yl)-1,3-thiazol-2-yl]amino}ethyl]-7-(propan-2-yloxy)-1,2-dihydroquinolin-2-one,
6-chloro-3-[(1S)-1-({5-[1-(cyclopropylmethyl)-1H-imidazol-5-yl]-1,3-thiazol-2-yl}amino)ethyl]-7-(propan-2-yloxy)-1,2-dihydroquinolin-2-one,
3-{[(1S)-1-[6-chloro-2-oxo-7-(propan-2-yloxy)-1,2-dihydroquinolin-3-yl]ethyl]amino}-1-methyl-1H-pyrazole-5-carboxamide,
2-{[(1S)-1-[6-chloro-2-oxo-7-(propan-2-yloxy)-1,2-dihydroquinolin-3-yl]ethyl]amino}-1H-imidazole-5-carboxamide,
N-(2-{[(1S)-1-[6-chloro-2-oxo-7-(propan-2-yloxy)-1,2-dihydroquinolin-3-yl]ethyl]amino}-1,3-oxazol-4-yl)acetamide,
2-{[(1S)-1-(6-chloro-7-cyclopropyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1,3-thiazole-5-carbonitrile,
2-{[(1S)-1-(6-chloro-7-cyclopropyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-4-methyl-1,3-thiazole-5-carbonitrile,
2-{[(1S)-1-(6-chloro-7-cyclopropyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-4-methoxy-1,3-thiazole-5-carbonitrile,
6-chloro-7-cyclopropyl-3-[(1S)-1-{[5-(2-oxo-1,3-oxazolidin-3-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
methyl N-(2-{[(1S)-1-(6-chloro-7-cyclopropyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1,3-thiazol-5-yl)carbamate,
2-{[(1S)-1-(6-chloro-7-cyclopropyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-4-methyl-1,3-thiazole-5-carboxamide,
6-chloro-7-cyclopropyl-3-[(1S)-1-{[5-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
6-chloro-7-cyclopropyl-3-[(1S)-1-{[5-(5-methyl-1H-1,2,3-triazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
6-chloro-7-cyclopropyl-3-[(1S)-1-{[5-(5-cyclopropyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
6-chloro-7-cyclopropyl-3-[(1S)-1-{[5-(5-cyclopropyl-1H-1,2,3-triazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
6-chloro-7-cyclopropyl-3-[(1S)-1-{[4-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
6-chloro-7-cyclopropyl-3-[(1S)-1-{[4-(5-methyl-1H-1,2,3-triazol-1-yl)-1,3-oxazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
6-chloro-7-cyclopropyl-3-[(1S)-1-{[4-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-oxazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
6-chloro-7-cyclopropyl-3-[(1S)-1-{[4-(pyridin-3-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
6-chloro-7-cyclopropyl-3-[(1S)-1-{[4-(pyridin-3-yl)-1,3-oxazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
3-{[(1S)-1-(6-chloro-7-cyclopropyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1-methyl-1H-1,2,4-triazole-5-carboxamide,
6-chloro-7-cyclopropyl-3-[(1S)-1-{[5-(1-cyclopropyl-1H-imidazol-5-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
6-chloro-7-cyclopropyl-3-[(1S)-1-({5-[1-(cyclopropylmethyl)-1H-imidazol-5-yl]-1,3-thiazol-2-yl}amino)ethyl]-1,2-dihydroquinolin-2-one,
3-{[(1S)-1-(6-chloro-7-cyclopropyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1-methyl-1H-pyrazole-5-carboxamide,
2-{[(1S)-1-(6-chloro-7-cyclopropyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1H-imidazole-5-carboxamide,
N-(2-{[(1S)-1-(6-chloro-7-cyclopropyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1,3-oxazol-4-yl)acetamide,
2-{[(1S)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-4-methoxy-1,3-thiazole-5-carbonitrile,
6-chloro-3-[(1S)-1-{[5-(2-oxo-1,3-oxazolidin-3-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
methyl N-(2-{[(1S)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1,3-thiazol-5-yl)carbamate,
6-chloro-3-[(1S)-1-{[5-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
6-chloro-3-[(1S)-1-{[5-(5-methyl-1H-1,2,3-triazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
6-chloro-3-[(1S)-1-{[5-(5-cyclopropyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
6-chloro-3-[(1S)-1-{[5-(5-cyclopropyl-1H-1,2,3-triazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
6-chloro-3-[(1S)-1-{[4-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
6-chloro-3-[(1S)-1-{[4-(5-methyl-1H-1,2,3-triazol-1-yl)-1,3-oxazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
6-chloro-3-[(1S)-1-{[4-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-oxazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one
6-chloro-3-[(1S)-1-{[4-(pyridin-3-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
6-chloro-3-[(1S)-1-{[4-(pyridin-3-yl)-1,3-oxazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
3-{[(1S)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-ypethyl]amino}-1-methyl-1H-1,2,4-triazole-5-carboxamide,

6-chloro-3-[(1S)-1-{[5-(1-cyclopropyl-1H-imidazol-5-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1S)-1-({5-[1-(cyclopropylmethyl)-1H-imidazol-5-yl]-1,3-thiazol-2-yl}amino)ethyl]-1,2-dihydroquinolin-2-one,

3-{[(1S)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1-methyl-1H-pyrazole-5-carboxamide,

2-{[(1S)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1H-imidazole-5-carboxamide, and

N-(2-{[(1S)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1,3-oxazol-4-yl)acetamide.

In another embodiment of the invention, the compounds of Formula (I) are enantiomers. In some embodiments the compounds are the (S)-enantiomer. In other embodiments the compounds are the (R)-enantiomer. In yet other embodiments, the compounds of Formula (I) may be (+) or (−) enantiomers.

In another embodiment of the invention, the compounds of Formula I contain isotopes of atoms forming the structure of Formula I. Isotopes herein means, each of two or more forms of the same element (e.g., H and D; ^{12}C and ^{13}C) that contain equal numbers of protons but different numbers of neutrons in their nuclei, and hence differ in relative atomic mass.

It should be understood that all isomeric forms are included within the present invention, including mixtures thereof. If the compound contains a double bond, the substituent may be in the E or Z configuration. If the compound contains a disubstituted cycloalkyl, the cycloalkyl substituent may have a cis- or trans configuration. All tautomeric forms are also intended to be included.

Method of Synthesizing the Compounds

The compounds of the present invention may be made by a variety of methods, including standard chemistry. Suitable synthetic routes are depicted in the Schemes given below.

The compounds of Formula (I) may be prepared by methods known in the art of organic synthesis as set forth in part by the following synthetic schemes. In the schemes described below, it is well understood that protecting groups for sensitive or reactive groups are employed where necessary in accordance with general principles or chemistry. Protecting groups are manipulated according to standard methods of organic synthesis (T. W. Greene and P. G. M. Wuts, “Protective Groups in Organic Synthesis”, Third edition, Wiley, New York 1999). These groups are removed at a convenient stage of the compound synthesis using methods that are readily apparent to those skilled in the art. The selection processes, as well as the reaction conditions and order of their execution, shall be consistent with the preparation of compounds of Formula (I).

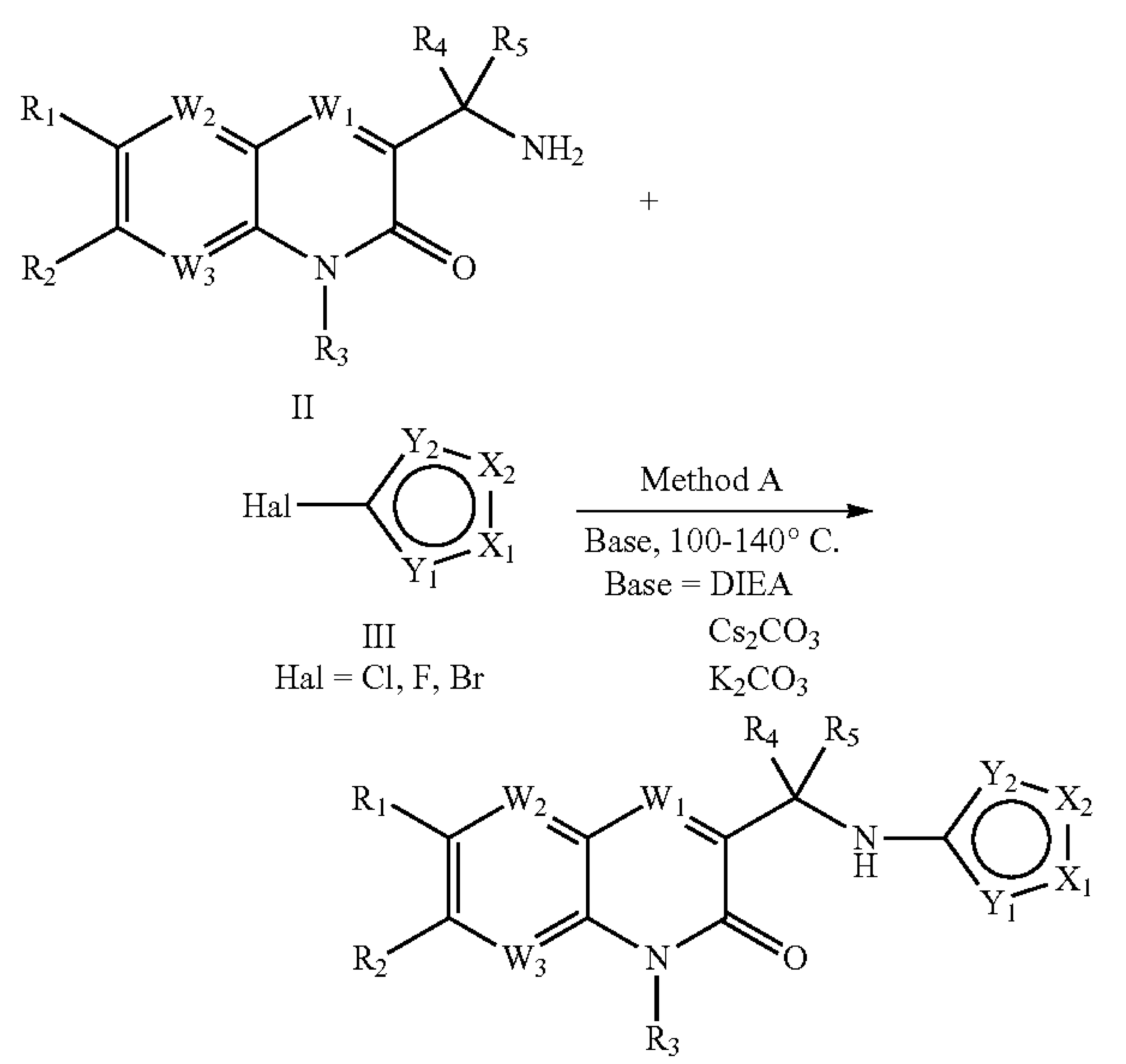
Those skilled in the art will recognize if a stereocenter exists in the compounds of Formula (I). Accordingly, the present invention includes both possible stereoisomers (unless specified in the synthesis) and includes not only racemic compounds but the individual enantiomers and/or diastereomers as well. When a compound is desired as a single enantiomer or diastereomer, it may be obtained by stereospecific synthesis or by resolution of the final product or any convenient intermediate. Resolution of the final product, an intermediate, or a starting material may be affected by any suitable method known in the art. See, for example, “Stereochemistry of Organic Compounds” by E. L. Eliel, S. H. Wilen, and L. N. Mander (Wiley-Interscience, 1994).

The compounds described herein may be made from commercially available starting materials or synthesized using known organic, inorganic, and/or enzymatic processes.

Preparation of Compounds

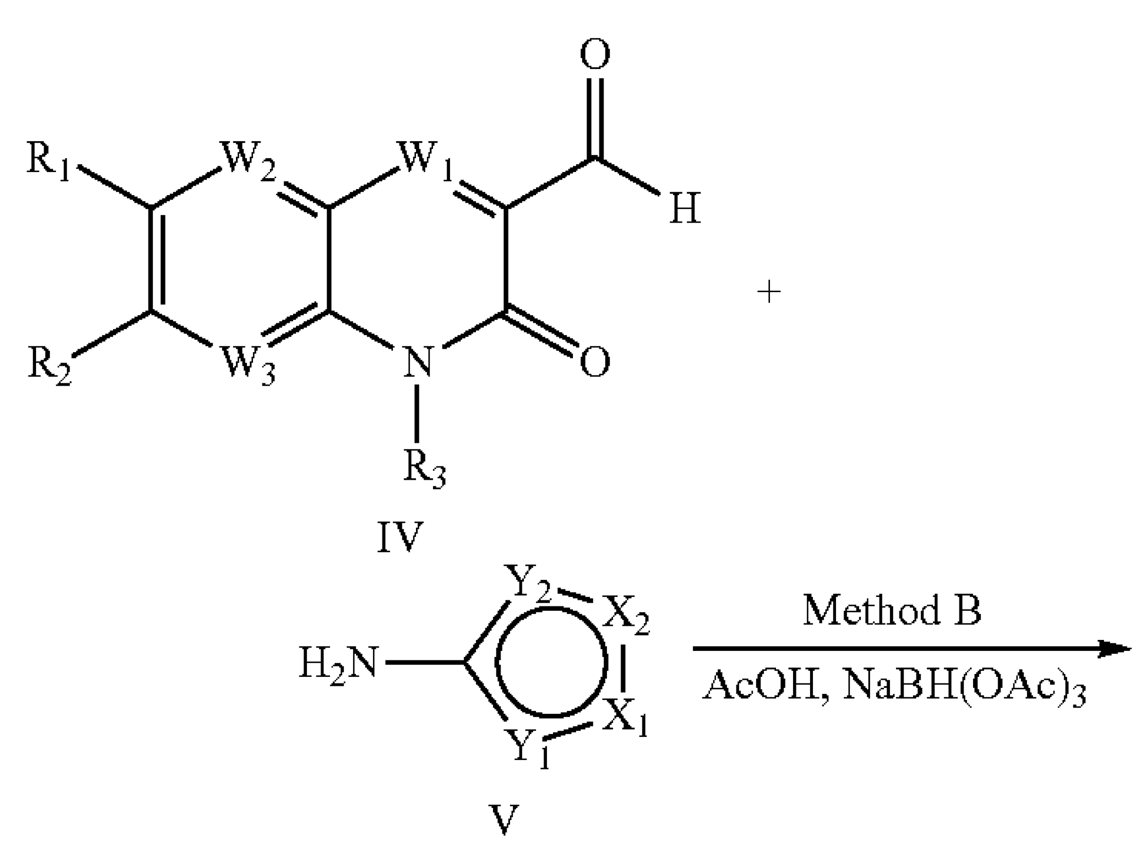
The compounds of the present invention can be prepared in a number of ways well known to those skilled in the art of organic synthesis. By way of example, compounds of the present invention can be synthesized using the methods described below, together with synthetic methods known in the art of synthetic organic chemistry, or variations thereon as appreciated by those skilled in the art. Preferred methods include but are not limited to those methods described below. Compounds of the present invention formula (I) can be synthesized by following the steps outlined in Schemes 1-2, which comprise different sequences of assembling intermediates II, III, IV, and V. Starting materials are either commercially available or made by known procedures in the reported literature or as illustrated.

Scheme 1



wherein W_1-W_3, X_1, X_2, Y_1, Y_2, and R_1-R_5 are defined in Formula (I)

Scheme 2



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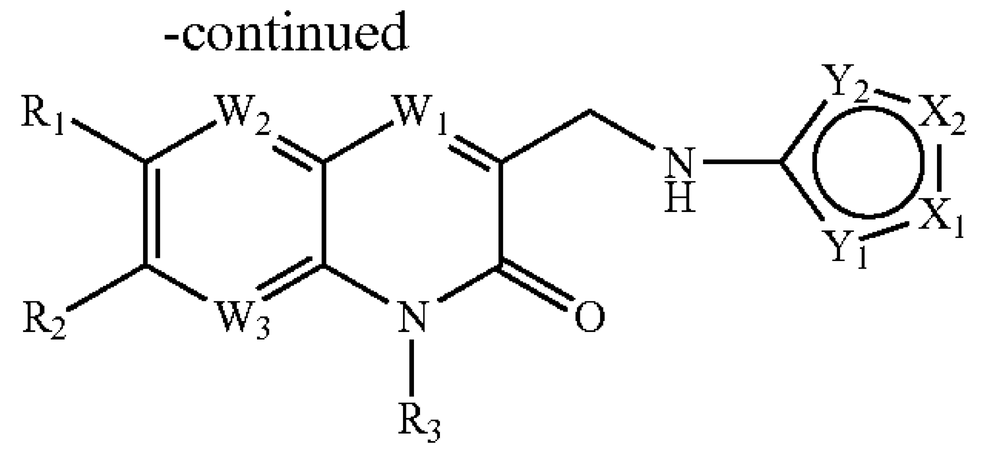


I

wherein W_1-W_3, X_1, X_2, Y_1, Y_2, R_1-R_3 are defined in Formula (I), and R_4 and R_5 are H.

The general ways of preparing target molecules of Formula I by using intermediates II, III, IV and V are outlined in Scheme 1-2. Displacement of aryl halides (III) with intermediates amine (II) under standard nucleophilic substitution conditions using base such as N,N-diisopropylethylamine, and/or potassium carbonate, cesium carbonate in solvent DMSO or DMF gives the compounds of Formula I. Reductive amination of aldehyde (IV) with amine (V) is performed under standard procedure (AcOH and $NaBH(OAc)_3$) to prepare the compound of formula I. A mixture of enantiomers, diastereomers, cis/trans isomers resulted from the process can be separated into their single components by chiral salt technique, chromatography using normal phase, reverse phase or chiral column, depending on the nature of the separation.

It should be understood that in the description and formulae shown above, the various groups W_1, W_2, W_3, X_1, X_2, Y_1, Y_2, R_1-R_5 and other variables are as defined above, except where otherwise indicated. Furthermore, for synthetic purposes, the compounds of schemes 1 and 2 are mere representative with elected radicals to illustrate the general synthetic methodology of the compound of formula I as defined herein.

Methods of Using the Disclosed Compounds

Another aspect of the invention relates to a method of treating a disease or disorder associated with mutant isocitrate dehydrogenase. The method involves administering to a patient in need of a treatment for diseases or disorders associated with mutant isocitrate dehydrogenase an effective amount of the compositions and compounds of Formula (I).

Another aspect of the invention is directed to a method of inhibiting mutant isocitrate dehydrogenase. The method involves administering to a patient in need thereof an effective amount of a compound of Formula (I).

Examples of a mutant IDH protein having a neomorphic activity are mutant IDH1 and mutant IDH2. A neomorphic activity associated with mutant IDH1 and mutant IDH2 is the ability to produce 2-hydroxyglutarate (2-HG neomorphic activity), specifically R-2-HG (R-2-HG neomorphic activity). Mutations in IDH 1 associated with 2-HG neomorphic activity, specifically R-2-HG neomorphic activity, include mutations at residues 97, 100, and 132, e.g. G97D, R100Q, R132H, R132C, R132S, R132G, R132L, and R132V. Mutations in IDH2 associated with 2-HG neoactivity, specifically R-2-HG neomorphic activity, include mutations at residues 140 and 172, e.g. R140Q, R140G, R172K, R172M, R172S, R172G, and R172W.

Another aspect of the invention relates to method of reducing 2-hydroxyglutarate. The method comprises administering to a patient in need thereof an effective amount of a compound of Formula (I).

One therapeutic use of the compounds or compositions of the present invention which inhibit mt-IDH is to provide treatment to patients or subjects suffering from cell proliferative diseases and cancers including, without limitation, glioma, glioblastoma multiforme, paraganglioma, supratentorial primordial neuroectodermal tumors, acute myeloid leukemia (AML), prostate cancer, thyroid cancer, colon cancer, chondrosarcoma, cholangiocarcinoma, peripheral T-cell lymphoma, melanoma, intrahepatic cholangiocarcinoma (IHCC), myelodysplastic syndrome (MDS), myeloproliferative disease (MPD), and other solid tumors. Targeted treatments for these cancers and cell proliferative diseases are not currently available to patients suffering from these conditions. Therefore, there is a need for new therapeutic agents selective to these conditions.

The disclosed compounds of the invention can be administered in effective amounts to treat or prevent a disorder and/or prevent the development thereof in subjects.

Administration of the disclosed compounds can be accomplished via any mode of administration for therapeutic agents. These modes include systemic or local administration such as oral, nasal, parenteral, transdermal, subcutaneous, vaginal, buccal, rectal or topical administration modes.

Depending on the intended mode of administration, the disclosed compositions can be in solid, semi-solid or liquid dosage form, such as, for example, injectables, tablets, suppositories, pills, time-release capsules, elixirs, tinctures, emulsions, syrups, powders, liquids, suspensions, or the like, sometimes in unit dosages and consistent with conventional pharmaceutical practices. Likewise, they can also be administered in intravenous (both bolus and infusion), intraperitoneal, subcutaneous or intramuscular form, and all using forms well known to those skilled in the pharmaceutical arts.

Illustrative pharmaceutical compositions are tablets and gelatin capsules comprising a Compound of the Invention and a pharmaceutically acceptable carrier, such as a) a diluent, e.g., purified water, triglyceride oils, such as hydrogenated or partially hydrogenated vegetable oil, or mixtures thereof, corn oil, olive oil, sunflower oil, safflower oil, fish oils, such as EPA or DHA, or their esters or triglycerides or mixtures thereof, omega-3 fatty acids or derivatives thereof, lactose, dextrose, sucrose, mannitol, sorbitol, cellulose, sodium, saccharin, glucose and/or glycine; b) a lubricant, e.g., silica, talcum, stearic acid, its magnesium or calcium salt, sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and/or polyethylene glycol; for tablets also; c) a binder, e.g., magnesium aluminum silicate, starch paste, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, magnesium carbonate, natural sugars such as glucose or beta-lactose, corn sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, waxes and/or polyvinylpyrrolidone, if desired; d) a disintegrant, e.g., starches, agar, methyl cellulose, bentonite, xanthan gum, algic acid or its sodium salt, or effervescent mixtures; e) absorbent, colorant, flavorant and sweetener; f) an emulsifier or dispersing agent, such as Tween 80, Labrasol, HPMC, DOSS, caproyl 909, labrafac, labrafil, peceol, transcutol, capmul MCM, capmul PG-12, captex 355, gelucire, vitamin E TGPS or other acceptable emulsifier; and/or g) an agent that enhances absorption of the compound such as cyclodextrin, hydroxypropyl-cyclodextrin, PEG400, PEG200.

Liquid, particularly injectable, compositions can, for example, be prepared by dissolution, dispersion, etc. For example, the disclosed compound is dissolved in or mixed with a pharmaceutically acceptable solvent such as, for example, water, saline, aqueous dextrose, glycerol, ethanol, and the like, to thereby form an injectable isotonic solution or suspension. Proteins such as albumin, chylomicron particles, or serum proteins can be used to solubilize the disclosed compounds.

The disclosed compounds can be also formulated as a suppository that can be prepared from fatty emulsions or suspensions; using polyalkylene glycols such as propylene glycol, as the carrier.

The disclosed compounds can also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, containing cholesterol, stearylamine or phosphatidylcholines. In some embodiments, a film of lipid components is hydrated with an aqueous solution of drug to a form lipid layer encapsulating the drug, as described in U.S. Pat. No. 5,262,564.

Disclosed compounds can also be delivered by the use of monoclonal antibodies as individual carriers to which the disclosed compounds are coupled. The disclosed compounds can also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinylpyrrolidone, pyran copolymer, polyhydroxypropylmethacrylamide-phenol, polyhydroxyethylaspanamidephenol, or polyethyleneoxidepolylysine substituted with palmitoyl residues. Furthermore, the Disclosed compounds can be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross-linked or amphipathic block copolymers of hydrogels. In one embodiment, disclosed compounds are not covalently bound to a polymer, e.g., a polycarboxylic acid polymer, or a polyacrylate.

Parental injectable administration is generally used for subcutaneous, intramuscular or intravenous injections and infusions. Injectables can be prepared in conventional forms, either as liquid solutions or suspensions or solid forms suitable for dissolving in liquid prior to injection.

Another aspect of the invention is directed to pharmaceutical compositions comprising a compound of Formula (I) and a pharmaceutically acceptable carrier. The pharmaceutical acceptable carrier may further include an excipient, diluent, or surfactant.

Compositions can be prepared according to conventional mixing, granulating or coating methods, respectively, and the present pharmaceutical compositions can contain from about 0.1% to about 99%, from about 5% to about 90%, or from about 1% to about 20% of the disclosed compound by weight or volume.

The dosage regimen utilizing the disclosed compound is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal or hepatic function of the patient; and the particular disclosed compound employed. A physician or veterinarian of ordinary skill in the art can readily determine and prescribe the effective amount of the drug required to prevent, counter or arrest the progress of the condition.

Effective dosage amounts of the disclosed compounds, when used for the indicated effects, range from about 0.5 mg to about 5000 mg of the disclosed compound as needed to treat the condition. Compositions for in vivo or in vitro use can contain about 0.5, 5, 20, 50, 75, 100, 150, 250, 500, 750, 1000, 1250, 2500, 3500, or 5000 mg of the disclosed compound, or, in a range of from one amount to another amount in the list of doses. In one embodiment, the compositions are in the form of a tablet that can be scored.

EXAMPLES

The disclosure is further illustrated by the following examples and synthesis schemes, which are not to be construed as limiting this disclosure in scope or spirit to the specific procedures herein described. It is to be understood that the examples are provided to illustrate certain embodiments and that no limitation to the scope of the disclosure is intended thereby. It is to be further understood that resort may be had to various other embodiments, modifications, and equivalents thereof which may suggest themselves to those skilled in the art without departing from the spirit of the present disclosure and/or scope of the appended claims.

Table 5 provides activity of illustrative compounds of Formula I in IDH1-R132H, IDH1-R132C, IDH1-MS-HTC116-R132H, and IDH1-MS-HTC116-R132C assays.

Analytical Methods, Materials, and Instrumentation

Unless otherwise noted, reagents and solvents were used as received from commercial suppliers. Proton nuclear magnetic resonance (NMR) spectra were obtained on either Bruker or Varian spectrometers at 300 MHz. Spectra are given in ppm (δ) and coupling constants, J, are reported in Hertz. Tetramethylsilane (TMS) was used as an internal standard. Mass spectra were collected using a Waters ZQ Single Quad Mass Spectrometer (ion trap electrospray ionization (ESI)). High performance liquid chromatograph (HPLC) analyses were obtained using a XBridge Phenyl or C18 column (5 μm, 50×4.6 mm, 150×4.6 mm or 250×4.6 mm) with UV detection (Waters 996 PDA) at 254 nm or 223 nm using a standard solvent gradient program (Method 1-4).

LCMS Method 1 (ESI, 4 Min Method):

Instruments:	
HPLC: Waters HT2790 Alliance UV: Waters 996 PDA	MS: Waters ZQ Single Quad Mass Spectrometer
Conditions:	
Mobile phase A	95% water/5% methanol with 0.1% Formic Acid
Mobile phase B (B)	95% methanol/5% water with 0.1% Formic Acid
Column	XBridge Phenyl or C18, 5 μm 4.6 × 50 mm
Column temperature	Ambient
LC gradient	Linear 5-95% B in 2.5 min, hold 95% B to 3.5 min
LC Flow rate	3 mL/min
UV wavelength	220 nm and 254 nm
Ionization Mode	Electrospray Ionization; positive/negative

LCMS Method 2 (ESI, 10 Min Method):

Instruments:	
HPLC: Waters HT2790 Alliance UV: Waters 996 PDA	MS: Waters ZQ Single Quad Mass Spectrometer
Conditions:	
Mobile phase A (A)	95% water/5% methanol with 0.1% Formic Acid
Mobile phase B (B)	95% methanol/5% water with 0.1% Formic Acid
Column	XBridge C18, 5 μm 4.6 × 150 mm
Column temperature	Ambient
LC gradient	Linear 5-95% B in 5.5 min, hold 95% B to 7.5 min
LC Flow rate	1.2 mL/min
UV wavelength	220 nm and 254 nm
Ionization Mode	Electrospray Ionization; positive/negative

LCMS Method 3: (APCI, 20 Min)

Instruments and conditions:		
HPLC-Agilent 1100 series. Column: Agela Technologies Durashell C18, 3 μm, 4.6 × 50 mm,). Mobile Phase A: ACN + 0.1% TFA. Mobile Phase B: Water + 0.1% TFA.		
Gradient:	Time (min)	% B
	00	95
	15	05
	18	05
	20	95
Flow Rate: 1 mL/min. ColumnTemperature: Ambient. Detector: 254 nm.		

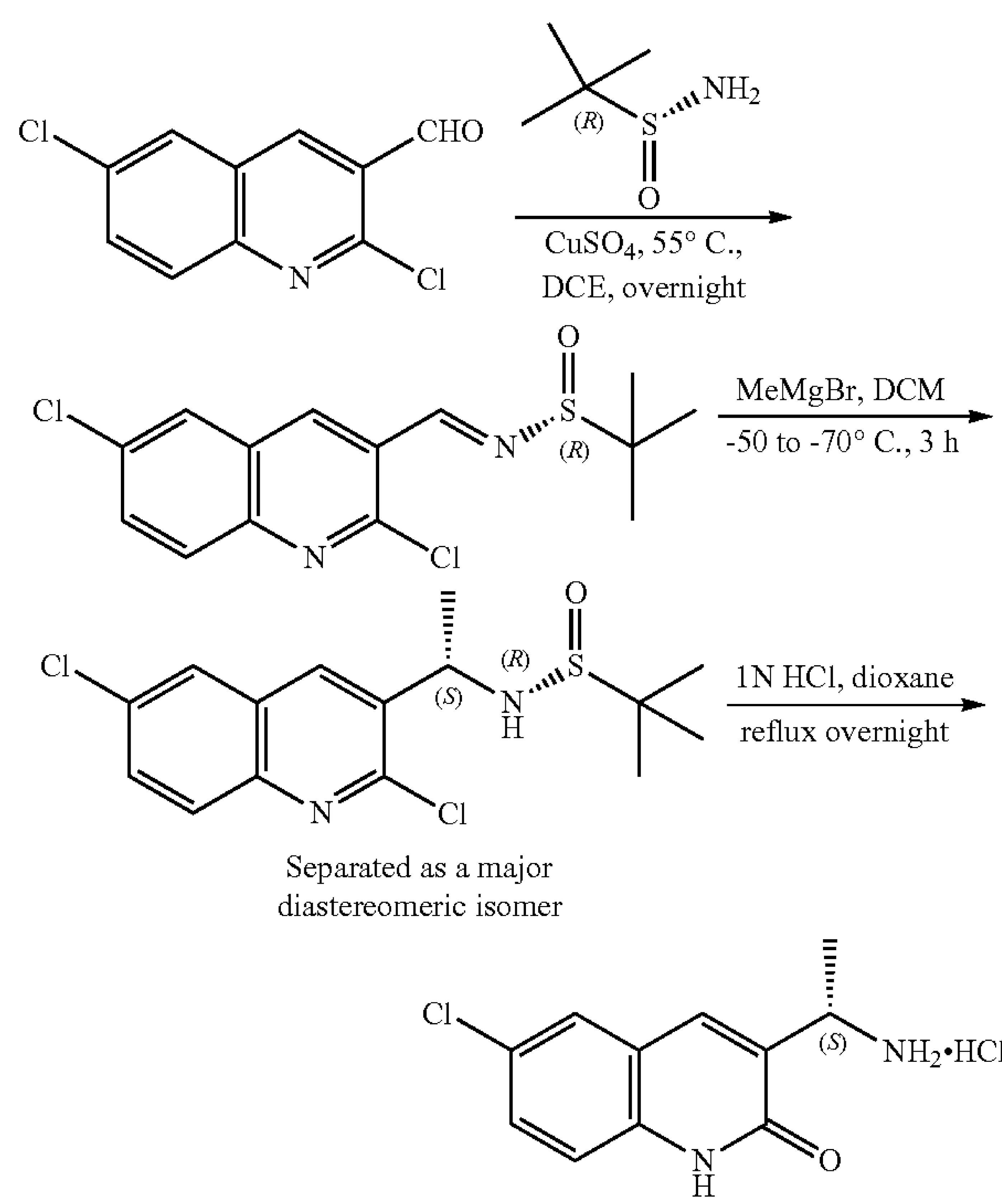
LCMS Method 4 (ESI, 2.5 Min Method):

Instruments and conditions:	
HPLC: Waters Acquity Binary Solvent Manager UV: Waters Acquity PDA	MS: Waters ZQ Mass Detector
Mobile phase A (A)	95% water/5% acetonitrile with 0.1% formic acid in 10 mM ammonium formate
Mobile phase B (B)	95% acetonitrile/5% water with 0.09% formic acid
Column	Waters Acquity UPLC BEH C18, 1.7 μm, 2.1 × 50 mm
Column temperature	35° C.
LC gradient	5-100% B in 2.0 min, hold 100% B to 2.2 min
LC Flow rate	0.6 mL/min
UV wavelength	220 nm and 254 nm
Ionization Mode	Electrospray Ionization; positive/negative

Abbreviations Used in the Following Examples and Elsewhere Herein are:

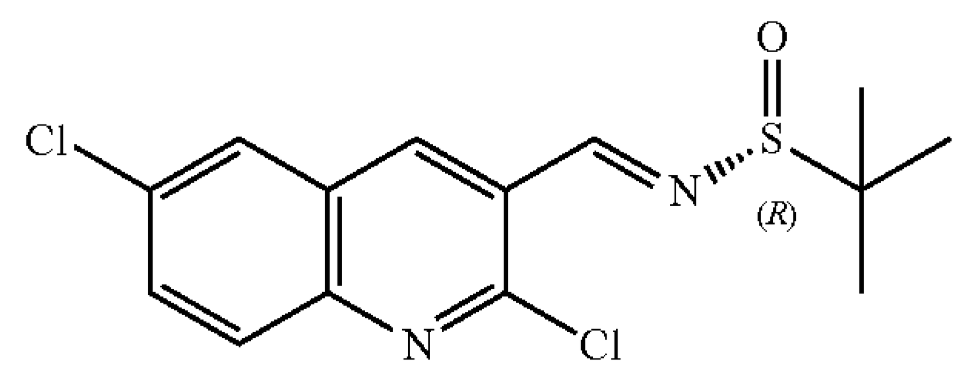
Ac_2O acetic anhydride
ACN Acetonitrile
BOP ammonium 4-(3-(pyridin-3-ylmethyl)ureido)benzenesulfinate
$CDCl_3$ deuterated chloroform
CDI 1,1'-Carbonyldiimidazole
Cs_2CO_3 cesium carbonate
$CuSO_4$ copper sulfate
δ chemical shift
DCM dichloromethane or methylene chloride
DCE 1,2-dichloroethane
DEAD diethyl azodicarboxylate
DIAD diisopropyl azodicarboxylate
DIEA N,N-diisopropylethylamine
DMA N,N-dimethylacetamide
DME dimethoxyethane
DMF N,N-dimethylformamide
DMP Dess-Martin Periodinane
DMSO dimethylsulfoxide
DMSO-d_6 deuterated dimethylsulfoxide
dppf 1,1'-Bis(diphenylphosphino)ferrocene
EDCI N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride
EDTA ethylenediaminetetraacetic acid
ee enantiomeric excess
EtOAc ethyl acetate
EtOH ethanol
^{1}H NMR proton nuclear magnetic resonance
HOAc acetic acid
HATU 2-(3H-[1,2,3]triazolo[4,5-b]pyridin-3-yl)-1,1,3,3-tetramethylisouronium hexafluorophosphate
HCl hydrochloric acid
HOBT 1H-benzo[d][1,2,3]triazol-1-ol hydrate
HPLC high pressure liquid chromatography
Hz hertz
IPA isopropyl alcohol
KOAc potassium acetate
K_2CO_3 potassium carbonate
LAH lithium aluminum hydride
LCMS liquid chromatography/mass spectrometry
(M+1) mass+1
m-CPBA m-chloroperbenzoic acid
MeOH methanol
MeMgBr methyl magnesium bromide
MS mass spectrometry
$NaBH_4$ sodium borohydride
Na_2SO_4 sodium sulfate
Pd(dppf)Cl_2 [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II)
Palladium tetrakis Tetrakis(triphenylphosphine)palladium (0)
Rt retention time
TBDMS-Cl Tert-butyl dimethylsilyl chloride
TEA triethylamine
TFA Trifluoroacetic acid
TFAA Trifluoroacetic anhydride
THF tetrahydrofuran
TLC thin layer chromatography
Xantphos 4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

Example 1—Intermediate II-1: (S)-3-(1-aminoethyl)-6-chloroquinolin-2-one hydrochloride



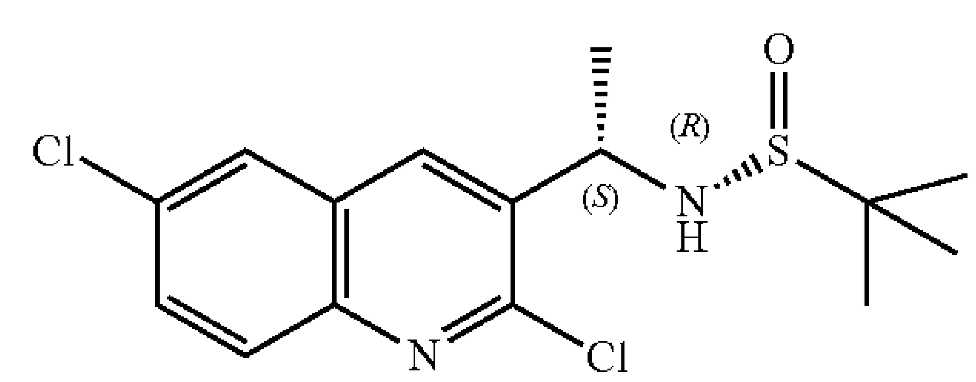
II-1

Step-1: (R,E)-N-((2,6-dichloroquinolin-3-yl)methylene)-2-methylpropane-2-sulfinamide



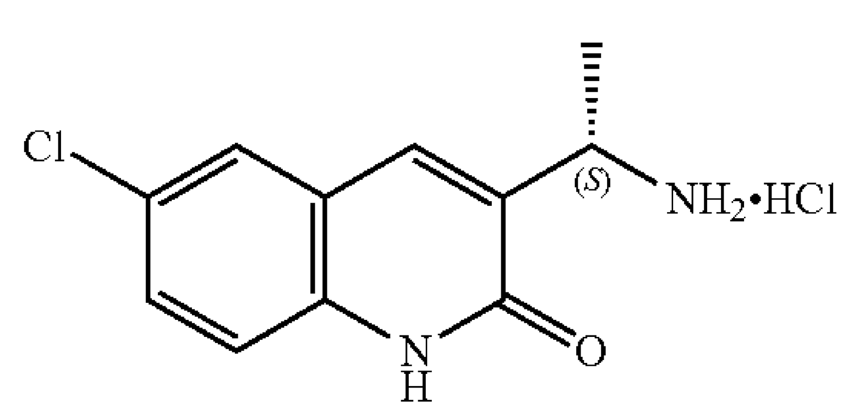
To a mixture of 2,6-dichloroquinoline-3-carbaldehyde (15.0 g, 66.37 mmol) and (R)-2-methylpropane-2-sulfinamide (8.85 g, 73.14 mmol) in 1,2-dichloroethane (150 mL) was added $CuSO_4$ (16.0 g, 100.25 mmol). The resulting mixture was heated to 55° C. and stirred at 55° C. overnight. After TLC and MS showed complete disappearance of starting materials, the mixture was cooled to room temperature and filtered through a pad of Celite®. The pad of celite was then rinsed with CH_2Cl_2. The filtrate was evaporated to dryness in vacuo and purified by SiO_2 column chromatography (0 to 25% hexanes/EtOAc) to afford the title compound, (R,E)-N-((2,6-dichloroquinolin-3-yl)methylene)-2-methylpropane-2-sulfinamide, as a yellow solid (17.7 g, 81% yield).

Step-2: (R)—N—((S)-1-(2,6-dichloroquinolin-3-yl)ethyl)-2-methylpropane-2-sulfinamide



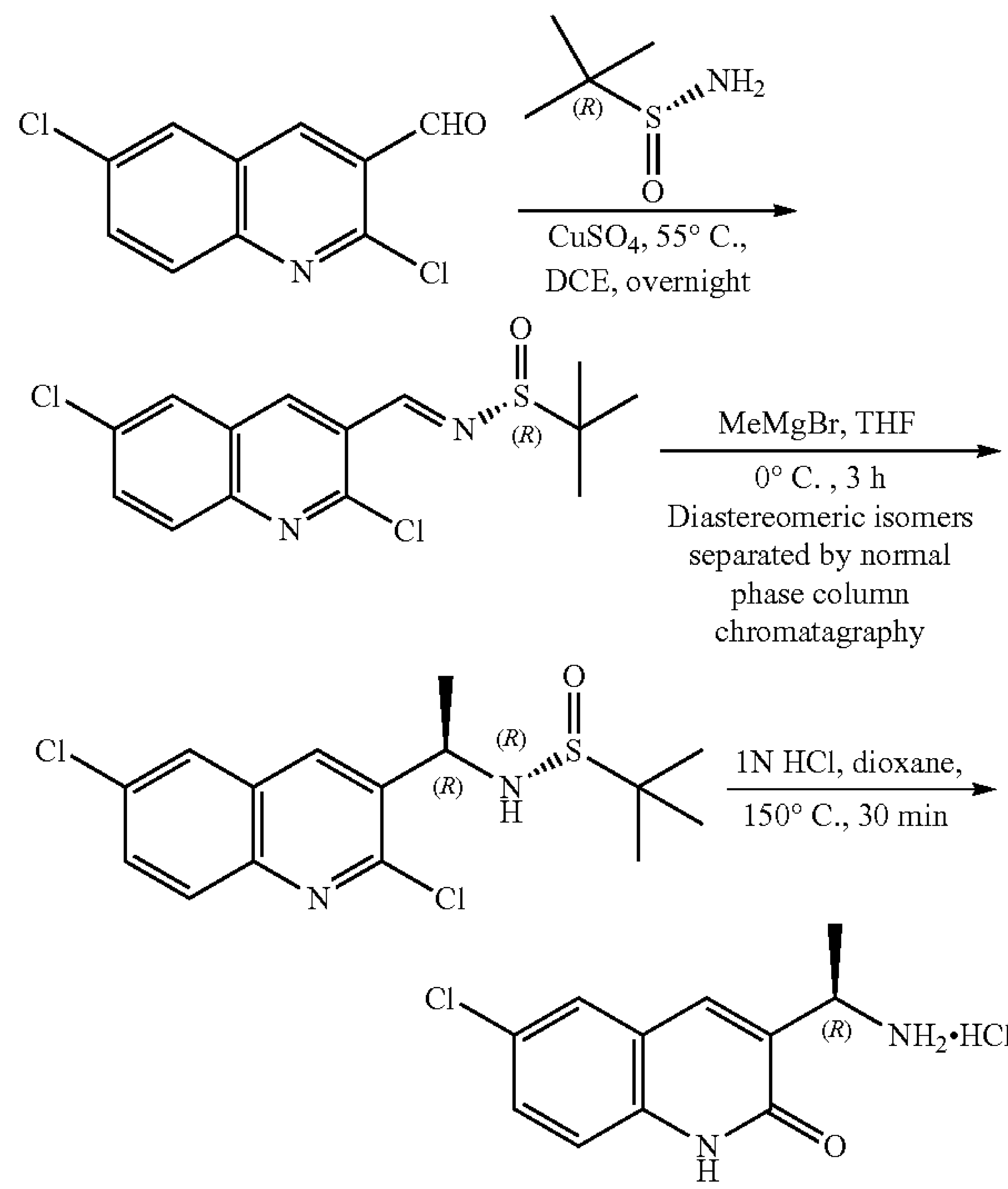
To a solution of (R,E)-N-((2,6-dichloroquinolin-3-yl)methylene)-2-methylpropane-2-sulfinamide (8.85 g, 26.88 mmol) in anhydrous CH_2Cl_2 (200 mL) at −60° C. was added drop wise MeMgBr (3M solution in diethyl ether, 13.5 mL, 40.54 mmol). The resulting reaction mixture was stirred at about −60 to −50° C. for 3 hours and then stirred at −20° C. overnight under an atmosphere of N_2. After TLC and MS showed complete disappearance of starting materials, saturated NH_4Cl (163 mL) was added at −20° C. and the resulting mixture was stirred for 10 minutes. The aqueous phase was extracted with CH_2Cl_2 (100 mL×3), dried over anhydrous Na_2SO_4, filtered, and evaporated. The residue was purified by column chromatography on an ISCO® chromatography system (SiO_2: Gold column; gradient; hexanes to 100% EtOAc) to provide the title compound, (R)—N—((S)-1-(2,6-dichloroquinolin-3-yl)ethyl)-2-methylpropane-2-sulfinamide, as a yellow solid (5.8 g, 63% yield).

Step-3: (S)-3-(1-aminoethyl)-6-chloroquinolin-2(1H)-one hydrochloride (II-1)



A mixture of (R)—N—((S)-1-(2,6-dichloroquinolin-3-yl)ethyl)-2-methylpropane-2-sulfinamide (6.6 g, 19.13 mmol) in 1,4-dioxane (41 mL) and 1N HCl (41 mL) was heated at reflux overnight. The solvents were evaporated in vacuo and the resulting residue was dissolved in hot water and lyophilized. The crude product was triturated with diethyl ether to afford the title compound II-1 as a yellow solid (9.0 g, ee: 98.4%). ^{1}H NMR (300 MHz, DMSO-d_6): δ ppm 12.4 (br s, 1H), 8.32 (br s, 2H), 8.07 (s, 1H), 7.85 (d, J=2.2 Hz, 1H), 7.63 (dd, J_1=8.8 Hz, J_2=2.5 Hz, 1H), 7.40 (d, J=8.8 Hz, 1H), 4.40-4.45 (m, 1H), 1.53 (d, J=8.5 Hz, 3H). LCMS (Method 3): Rt 3.42 min, m/z 223.1 $[M+H]^+$.

Example 2—Intermediate II-2: (R)-3-(1-(aminoethyl)-6-chloroquinolin-2(1H)-one hydrochloride



II-2

Step-1: (R)—N-((2,6-dichloroquinolin-3-yl)methylene)-2-methylpropane-2-sulfinamide

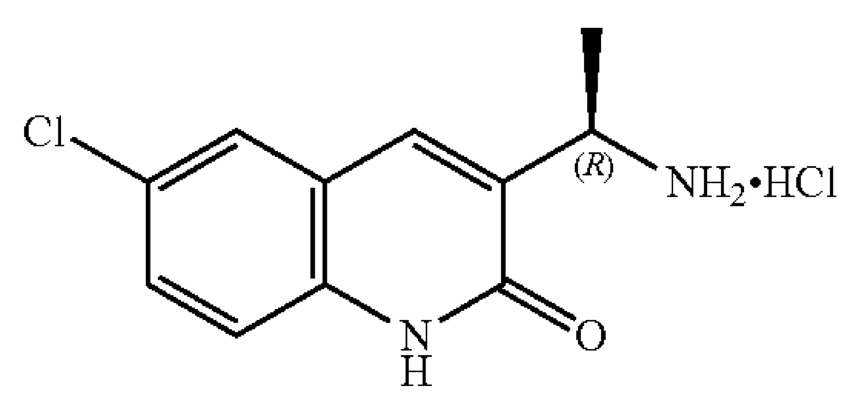
To a mixture of 2,6-dichloroquinoline-3-carbaldehyde (500 mg, 2.21 mmol) and (R)-2-methylpropane-2-sulfinamide (295 g, 2.43 mmol) in 1,2-dichloroethane (15 mL) was added $CuSO_4$ (530 mg, 3.31 mmol). The resulting mixture was heated to 55° C. and stirred at 55° C. for 18 hours. Once TLC and MS showed complete disappearance of starting materials, the reaction mixture was cooled to room temperature and filtered through a pad of Celite. The pad of celite was then rinsed with CH_2Cl_2. The filtrate was evaporated to dryness in vacuo and purified by column chromatography on an ISCO® chromatography system (SiO_2; hexanes to 60% EtOAc/hexanes) to afford the title compound, (R)—N-((2,6-dichloroquinolin-3-yl)methylene)-2-methylpropane-2-sulfinamide, as a yellow solid (510 mg, 70% yield).

Step-2: (R)—N—OR)-1-(2,6-dichloroquinolin-3-yl)ethyl)-2-methylpropane-2-sulfinamide

To a solution of (R)—N-((2,6-dichloroquinolin-3-yl)methylene)-2-methylpropane-2-sulfinamide (505 mg, 1.534

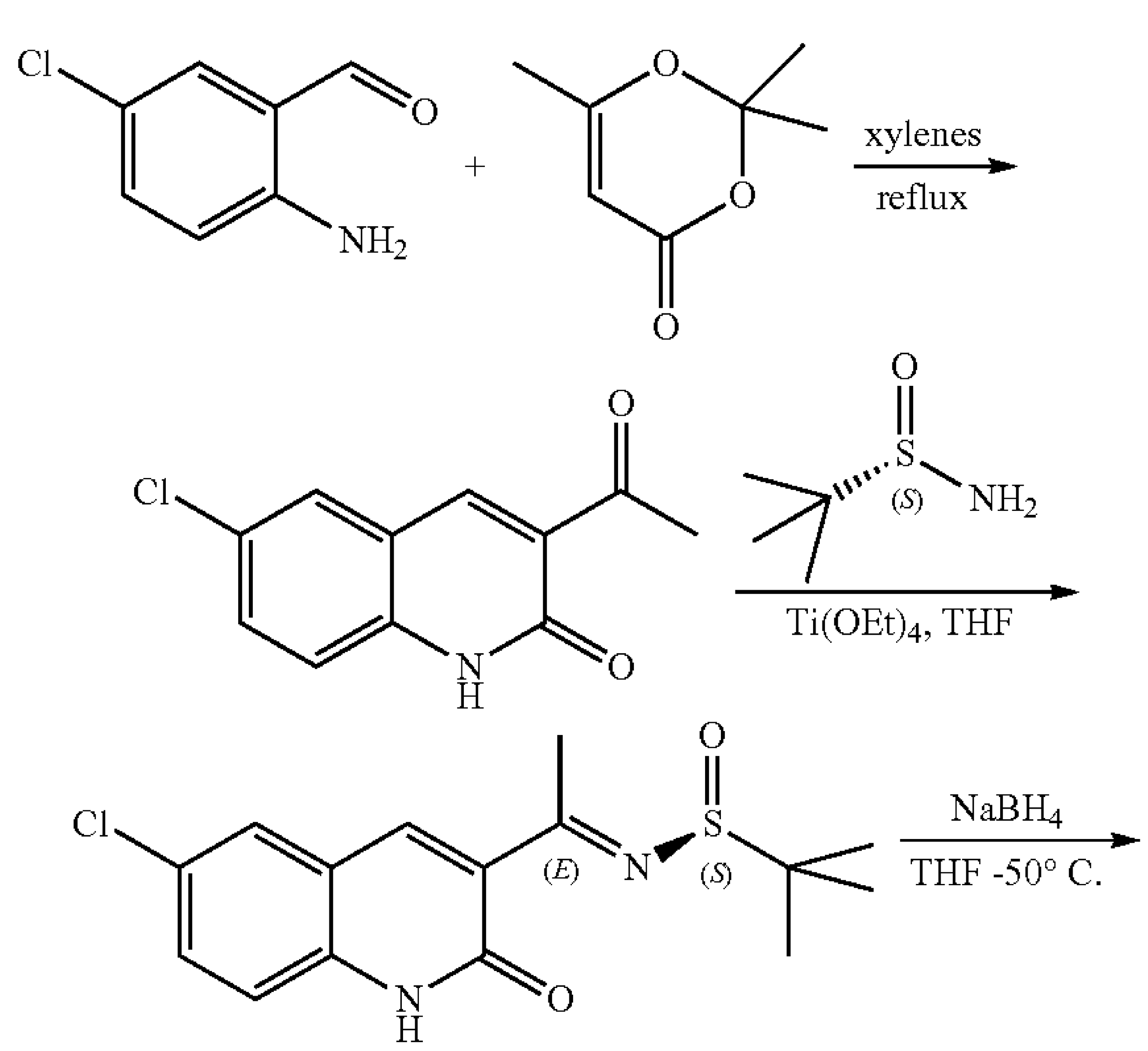
mmol) in anhydrous THF (8 mL) at 0° C. was added drop wise MeMgBr (3M solution in diethyl ether, 0.56 mL, 1.687 mmol). The mixture was stirred at 0° C. for 3 hours under an atmosphere of N_2. After TLC and MS showed complete disappearance of starting materials saturated NH_4Cl (5 mL) was added at 0° C. and the resulting mixture was stirred for 10 minutes. The aqueous phase was extracted with EtOAc (10 mL×3), dried over anhydrous Na_2SO_4, filtered, and evaporated. The residue was purified by column chromatography on an ISCO® chromatography system (SiO_2; hexanes to 80% EtOAc/hexanes) to afford the title compound as the R,R isomer as a pale yellow solid (200 mg, 38%) and the R,S isomer as a pale yellow solid (93 mg, 18% yield).

Step-3: (R)-3-(1-aminoethyl)-6-chloroquinolin-2(1H)-one hydrochloride (II-2)



A mixture of (R)—N—((R)-1-(2,6-dichloroquinolin-3-yl)ethyl)-2-methylpropane-2-sulfinamide (190 mg, 0.55 mmol) in 1,4-dioxane (2 mL) and 1N HCl (1.1 mL, 1.1 mmol) was heated to 150° C. for 30 minutes in a microwave reactor. The solvents were evaporated and the residue was dissolved in hot water and lyophilized to afford the title compound II-2 as a yellow solid (148 mg, quantitative yield). ^1H NMR (300 MHz, DMSO-d_6): δ ppm 12.35 (br s, 1H), 8.28 (br s, 2H), 8.05 (s, 1H), 7.86 (d, J=2.2 Hz, 1H), 7.63 (dd, J_1=8.8 Hz, J_2=2.5 Hz, 1H), 7.40 (d, J=8.8 Hz, 1H), 4.40-4.45 (m, 1H), 1.53 (d, J=8.5 Hz, 3H). LCMS (Method 3): Rt 3.40 min, m/z 223.1 $[M+H]^+$.

Example 3—an Alternative Approach to Intermediate II-1



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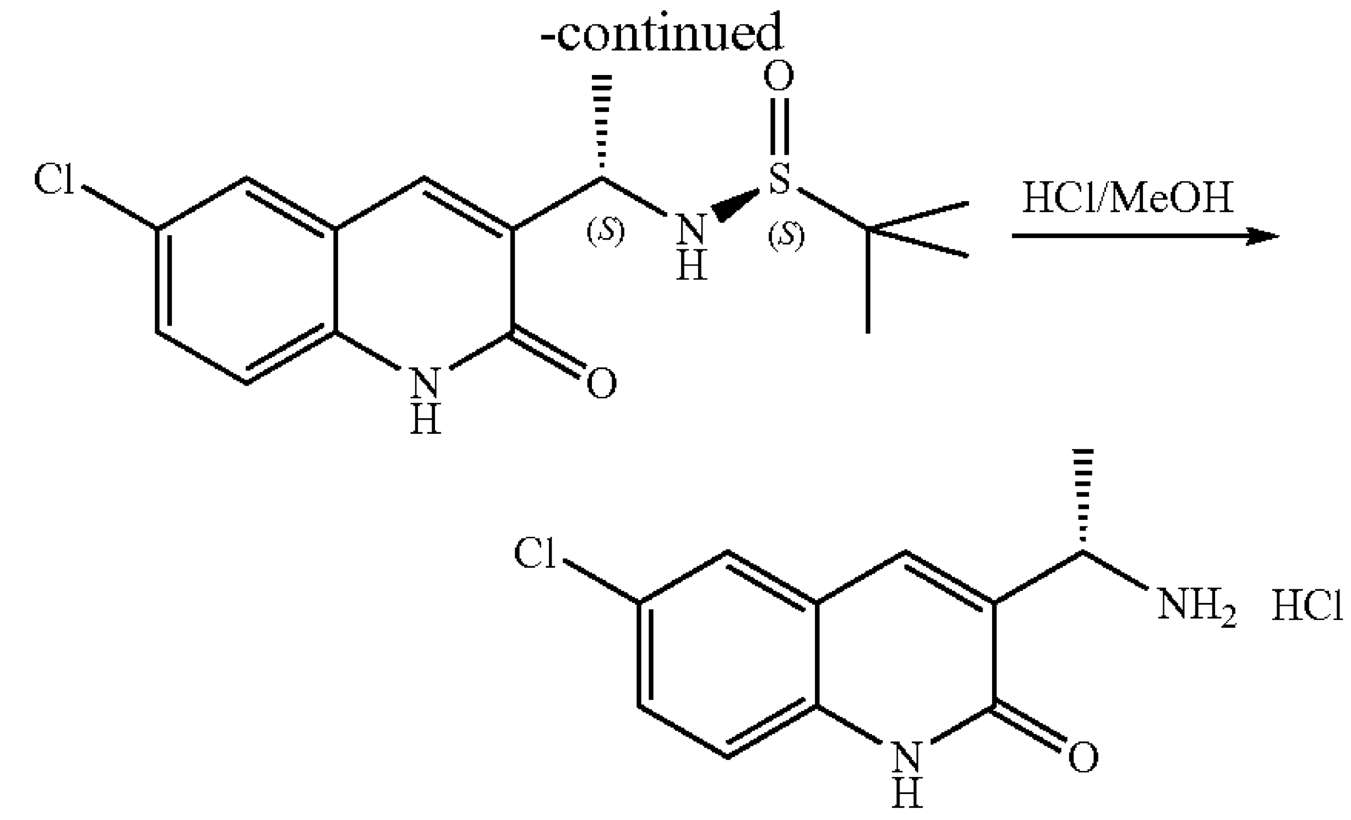
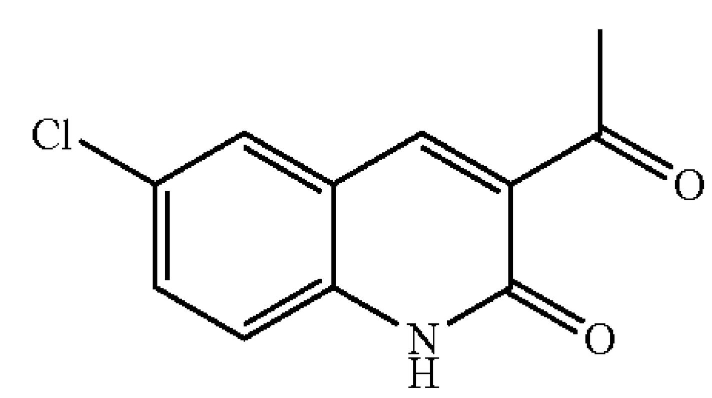


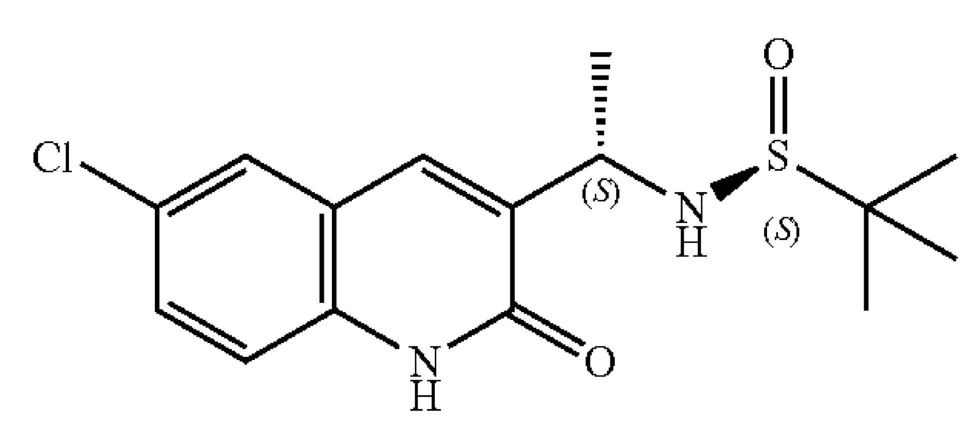
II-1
ee > 98%

Step-1: 3-acetyl-6-chloroquinolin-2(1H)-one



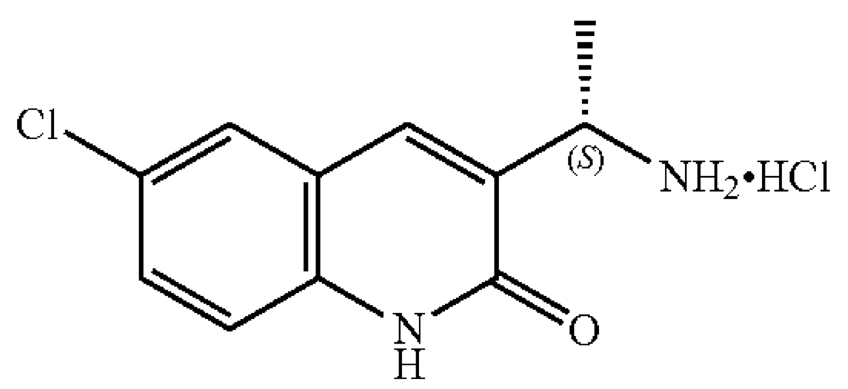
A mixture of 2-amino-5-chlorobenzaldehyde (0.5 g, 3.21 mmol) and 2,2,6-trimethyl-4H-1,3-dioxin-4-one (0.594 g, 4.18 mmol) in xylenes (10 mL) under an atmosphere of nitrogen was heated to reflux for 3 hours and then cooled to room temperature. The reaction mixture was filtered and washed with xylenes twice to afford the title compound, 3-acetyl-6-chloroquinolin-2(1H)-one (330 mg, 46.3%). ^1H NMR (300 MHz, DMSO-d_6): δ ppm 12.22 (br, 1H), 8.41 (s, 2H), 8.00 (s, 1H), 7.63 (d, J=8.8 Hz, 1H), 7.32 (dd, J_1=8.8 Hz, J_2=2.5 Hz, 1H), 2.58 (s, 3H). LCMS (Method 1): m/z 222.94 $[M+H]^+$.

Step-2: ((S)—N—((S)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)-2-methyl propane-2-sulfinamide



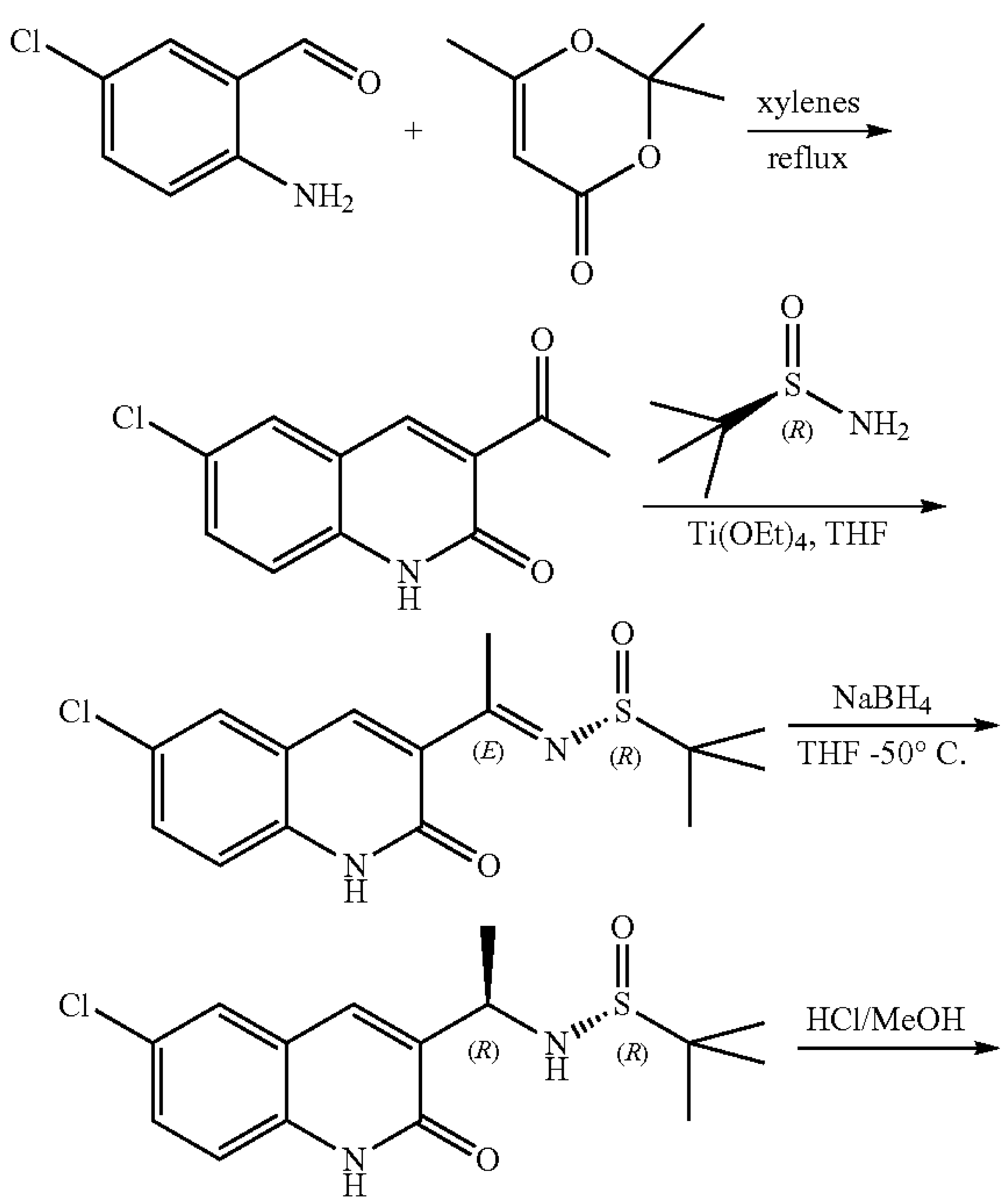
A mixture of tetraethoxytitanium (144 mg, 0.632 mmol), (S)-2-methylpropane-2-sulfinamide (38.3 mg, 0.316 mmol), and 3-acetyl-6-chloroquinolin-2(1H)-one (70 mg, 0.316 mmol) in THF (20 mL) was heated to 80° C. overnight and then cooled to room temperature. To this mixture was added $NaBH_4$ (59.7 mg, 1.579 mmol) at −50° C. The mixture was then slowly warmed up to room temperature overnight. MeOH (2 mL) was added to quench excess $NaBH_4$ and was followed by the addition of water. The resulting mixture was filtered to remove solids and the aqueous phase was extracted with EtOAc twice, dried over Na_2SO_4 and concentrated. The residue was purified on a Biotage® chromatography system using a 25 g SiO_2 column with gradient elution (20% to 100% EtOAc/Hexanes, then 0-5% MeOH/DCM) to afford (S)—N—((S)-1-(2,6-dichloroquinolin-3-yl)ethyl)-2-methylpropane-2-sulfinamide (39 mg, 38% yield). NMR (300 MHz, DMSO-d_6): δ ppm 12.05 (br, 1H), 7.95 (s, 1H), 7.84 (s, 1H), 7.38 (d, J=8.8 Hz, 1H), 5.76 (d, J=8.06 Hz, 1H), 5.37 (m, 1H), 4.55 (m, 1H), 1.44 (d, J=6.82 Hz, 3H), 1.18 (s, 9H). LCMS (Method 1): Rt 2.22 min; m/z 327.96 $[M+H]^+$.

Step-3: (S)-3-(1-aminoethyl)-6-chloroquinolin-2(1H)-one hydrochloride (III-1)



To a solution of ((S)—N—((S)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)-2-methyl propane-2-sulfinamide (150 mg, 0.459 mmol) in MeOH (5 mL) was added HCl (2 mL, 8.0 mmol, 4M in 1,4-dioxane). The mixture was stirred at room temperature overnight. To this mixture was added 6 mL of ethyl ether and the resulting precipitate was collected by filtration, washed with ethyl ether (2×), and then dried to afford (S)-3-(1-aminoethyl)-6-chloroquinolin-2(1R)-one hydrochloride, 114 (50 mg, 42% yield). ^1H NMR (300 MHz, DMSO-d_6): δ ppm 12.4 (br s, 1H), 8.32 (br s, 2H), 8.07 (s, 1H), 7.85 (d, J=2.2 Hz, 1H), 7.63 (dd, J_1=8.8 Hz, J_2=2.5 Hz, 1H), 7.40 (d, J=8.8 Hz, 1H), 4.40-4.45 (m, 1H), 1.53 (d, J=8.5 Hz, 3H). LCMS (Method 1): Rt 1.22 min, m/z 223.1 $[M+H]^+$.

Example 4—Alternate Approach (R)-3-(1-aminoethyl)-6-chloroquinolin-2(1H)-one hydrochloride (II-2)



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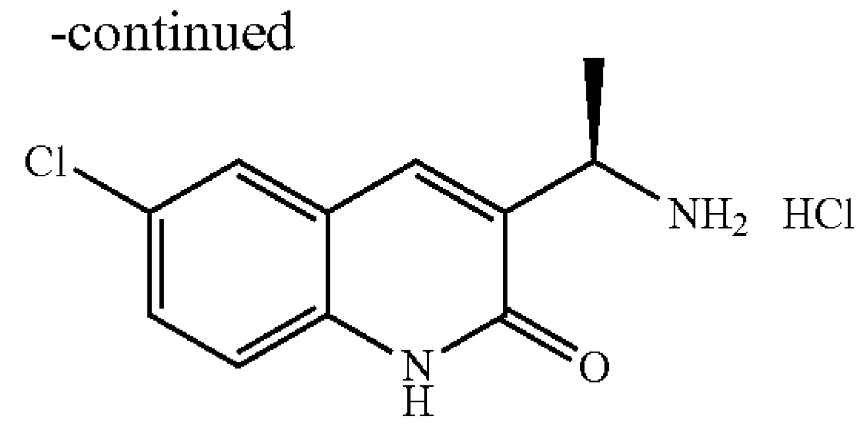
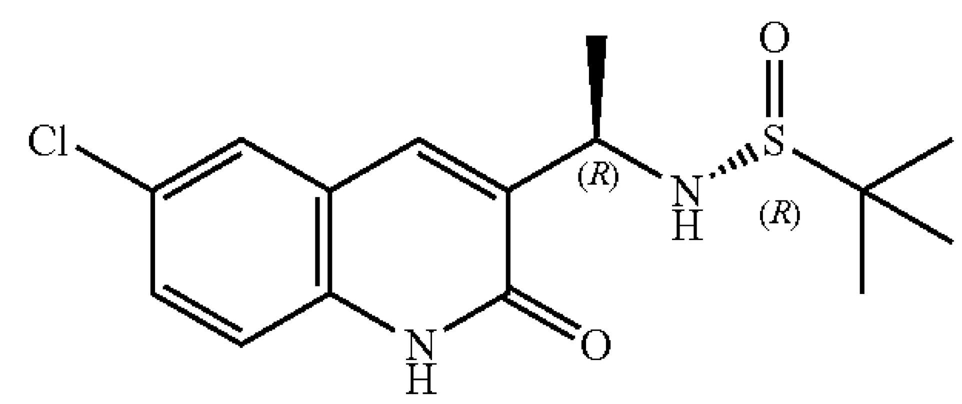


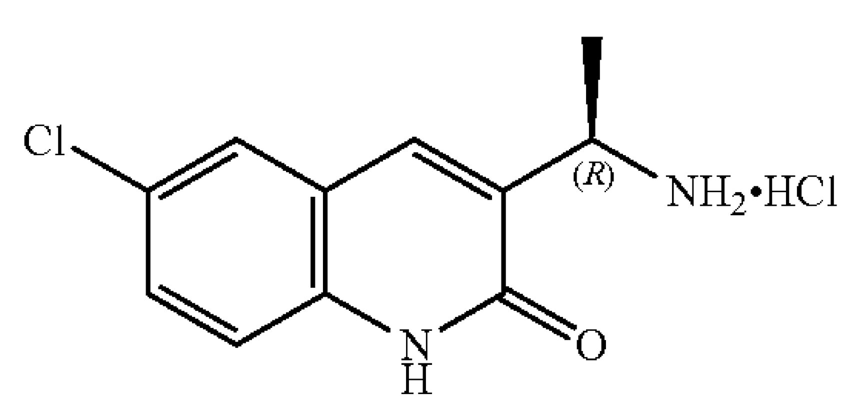
II-2
ee > 98%

Step-1: ((R)—N—((R)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)-2-methyl propane-2-sulfinamide



A mixture of tetraethoxytitanium (412 mg, 1.805 mmol) (R)-2-methylpropane-2-sulfinamide (131 mg, 1.083 mmol) and 3-acetyl-6-chloroquinolin-2(1H)-one (160 mg, 0.722 mmol) in THF (20 mL) was heated to 80° C. overnight, then cooled to room temperature. To this mixture was added $NaBH_4$ (137 mg, 3.61 mmol) −50° C. The mixture was then slowly warmed up to room temperature overnight. MeOH (2 mL) was added to quench excess $NaBH_4$ and was followed by the addition of water. The resulting mixture was filtered to remove solids and the aqueous phase was extracted with EtOAc twice, dried over Na_2SO_4 and concentrated. The residue was purified on a Biotage® chromatography system using a 25 g SiO_2 column with gradient elution (20 to 100% EtOAc/Hexanes, then 0-5% MeOH/DCM) to afford ((R)—N—((R)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)-2-methyl propane-2-sulfinamide (157 mg, 66% yield). ^1H NMR (300 MHz, $CDCl_3$): δ ppm 11.31 (br, 1H), 7.35 (s, 1H), 7.07-7.22 (m, 2H), 5.86 (d, J=9.3 Hz, 1H), 5.37 (m, 1H), 4.55 (m, 1H), 1.56 (d, J=6.94 Hz, 3H), 1.32 (s, 9H). LCMS (Method 1): Rt 2.20 min, m/z 327.96 $[M+H]^+$.

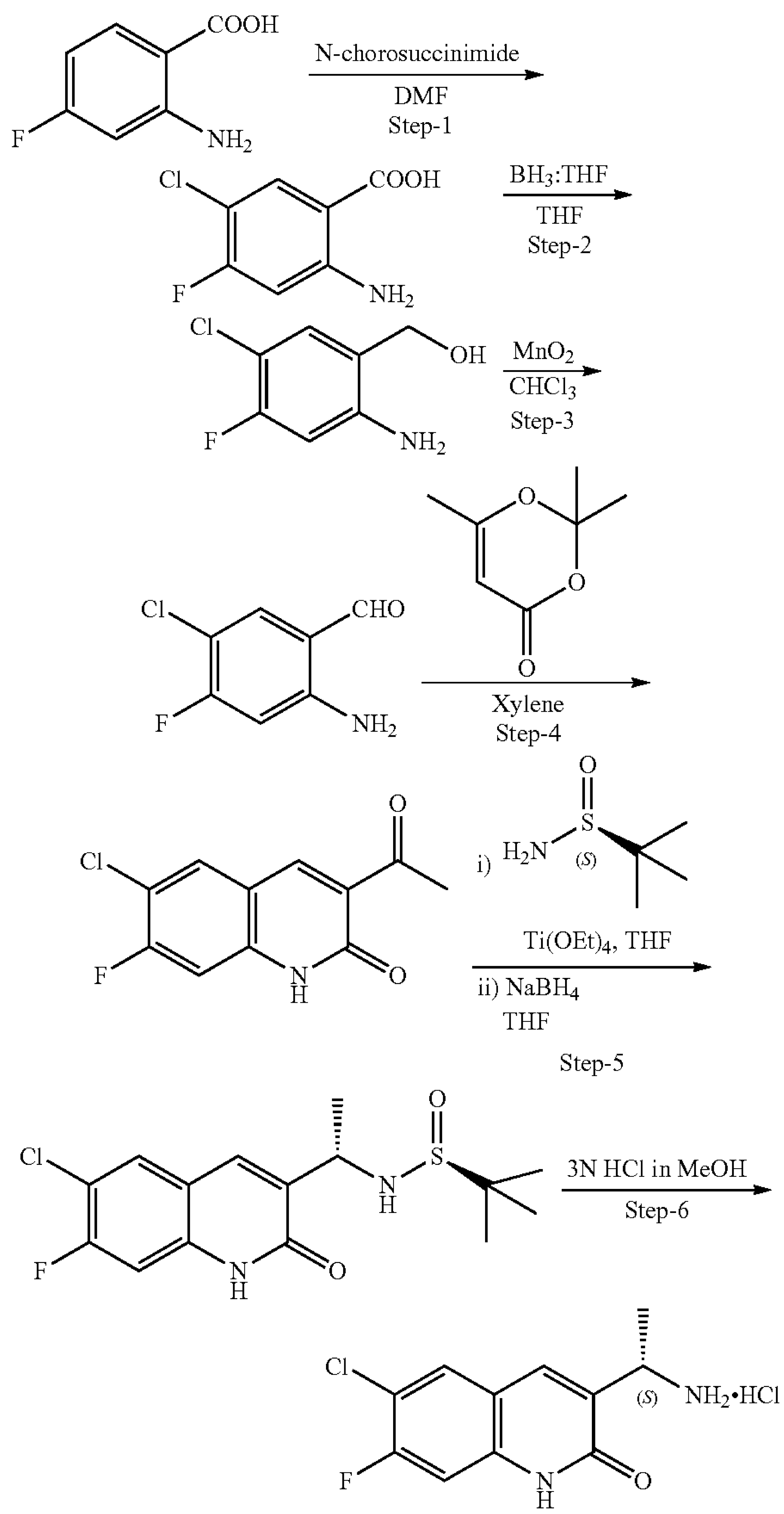
Step-2: (R)-3-(1-aminoethyl)-6-chloroquinolin-2(1H)-one hydrochloride (II-2)



To a solution of (R)—N—((R)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)-2-methylpropane-2-sulfinamide (150 mg, 0.459 mmol) in MeOH (5 mL) was added HCl (2 mL, 8.00 mmol, 4M in 1,4-dioxane). The mixture was stirred at room temperature overnight. To this mixture was added 6 mL of ethyl ether and the resulting precipitate was collected by filtration, washed with ethyl ether (2×), and then dried to afford (R)-3-(1-aminoethyl)-6-chloroquinolin-

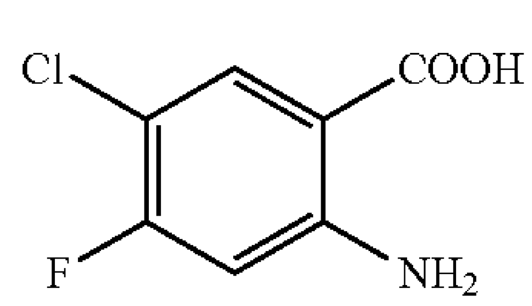
2(1H)-one hydrochloride (80 mg, 67% yield). [1]H NMR (300 MHz, DMSO-d_6): δ ppm 12.32 (br s, 1H), 8.34 (br, 2H), 8.06 (s, 1H), 7.81 (s, 1H), 7.58 (d, J=8.82 Hz, 1H), 7.31 (d, J=8.83 Hz, 1H), 4.40-4.45 (m, 1H), 1.53 (d, J=6.81 Hz, 3H). LCMS (Method 1): Rt 1.20 min, m/z 223.1 $[M+H]^+$.

Example 5—Intermediate II-3: (S)-3-(1-amino-ethyl)-6-chloro-7-fluoroquinolin-2(1H)-one (II-3)



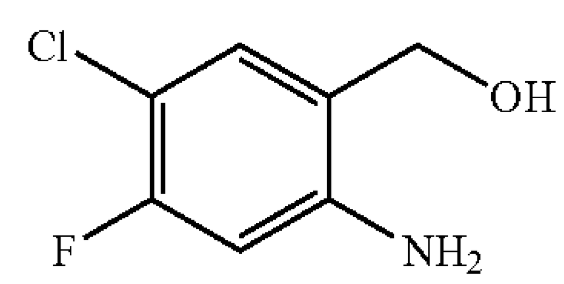
II-3

Step-1: 2-Amino-5-chloro-4-fluorobenzoic acid



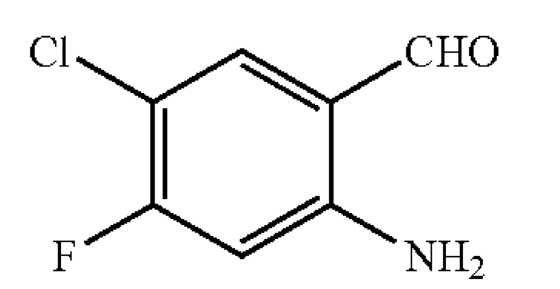
2-Amino-4-fluorobenzoic acid (50 g, 322.6 mmol) was dissolved in 700 mL of DMF and N-chlorosuccinimide (41 g, 305.5 mmol) was added portion wise. The reaction mixture was heated at 50° C. for 5 h. The mixture was cooled to room temperature, poured on to ice cold water to get the solid. The solid was filtered and dissolved in EtOAc, then sat. NaCl (300 mL) was added. The aqueous layer was extracted with EtOAc (3×200 mL). The combined organic phase was dried (Na_2SO_4) and evaporated to a brown solid (42 g, 69%) as desired product 2-amino-5-chloro-4-fluorobenzoic acid.

Step-2: (2-Amino-5-chloro-4-fluorophenyl)methanol



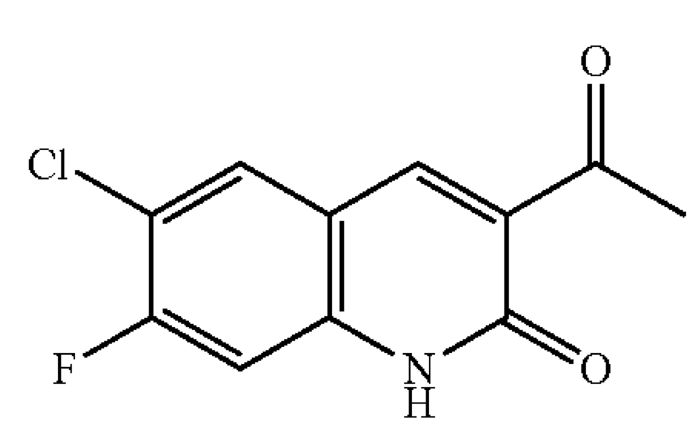
2-Amino-5-chloro-4-fluorobenzoic acid (42 g, 221 mmol) was dissolved in 100 mL of THF and BH_3.THF (712 mL of 1 M solution in THF, 712 mmol) was added drop wise over the period of 1 h at room temperature. The reaction mixture was heated at 50° C. overnight (18 h). The mixture was cooled to room temperature, poured onto ice cold water, and sat. NaCl solution was added. The aqueous was extracted with EtOAc (3×200 mL). The combined organic phase was dried (Na_2SO_4), evaporated and purified by flash chromatography using 0-100% hexanes/ethyl acetate as eluent to afford the desired product as a brown solid (17 g, 45%).

Step-3: 2-Amino-5-chloro-4-fluorobenzaldehyde



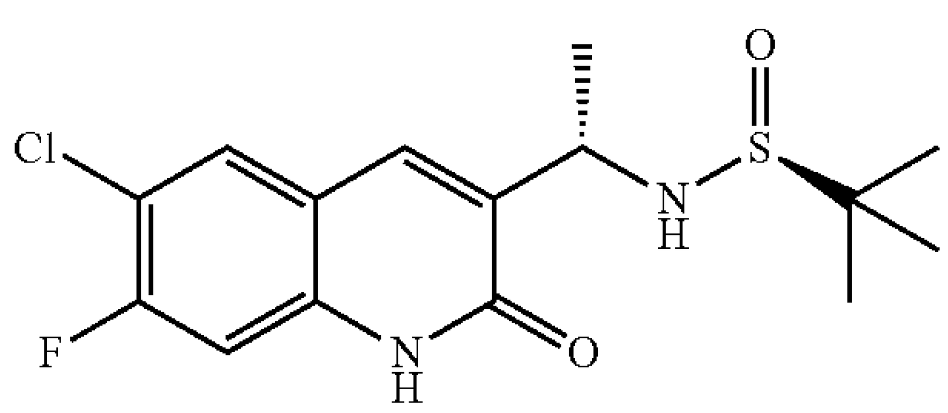
To a solution of (2-amino-5-chloro-4-fluorophenyl) methanol (22 g, 125.7 mmol) in 1000 mL of chloroform was added MnO_2 (109 g, 1250 mmol) and the reaction mixture was stirred overnight at ambient temperature. The reaction mixture was filtered, washed with EtOAc and evaporated. The resulting crude product was passed through a pad of silica gel eluting with 0 to 20% hexanes/EtOAc to give the pure product as a brown solid (19 g, 87%).

Step-4:
3-acetyl-6-chloro-7-fluoroquinolin-2(1H)-one



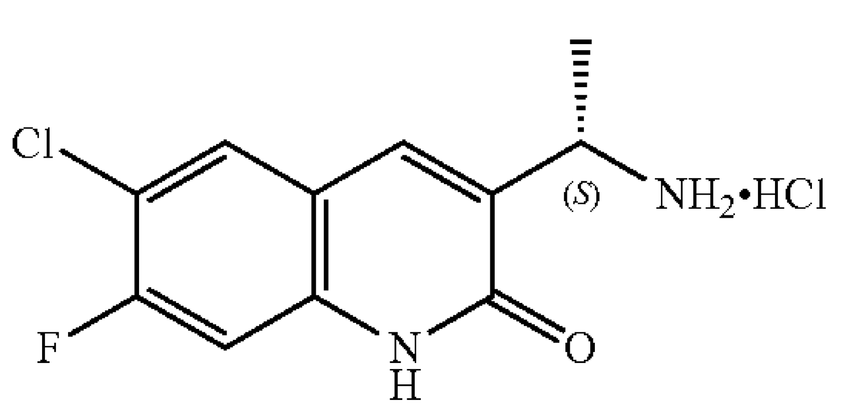
A mixture of 2-Amino-5-chloro-4-fluorobenzaldehyde (14 g, 173.6 mmol) and 2,2,6-trimethyl-4H-1,3-dioxin-4-one (16 mL, 121 mmol) in m-xylene (500 mL) was refluxed for 1.5 h. The reaction mixture was cooled to room temperature and filtered. The collected solid was washed with m-xylene and dried to yield the desired product (9.6 g, 50%) as off-white solid.

Step-5: (S)—N—((S)-1-(6-chloro-7-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)-2-methyl propane-2-sulfinamide



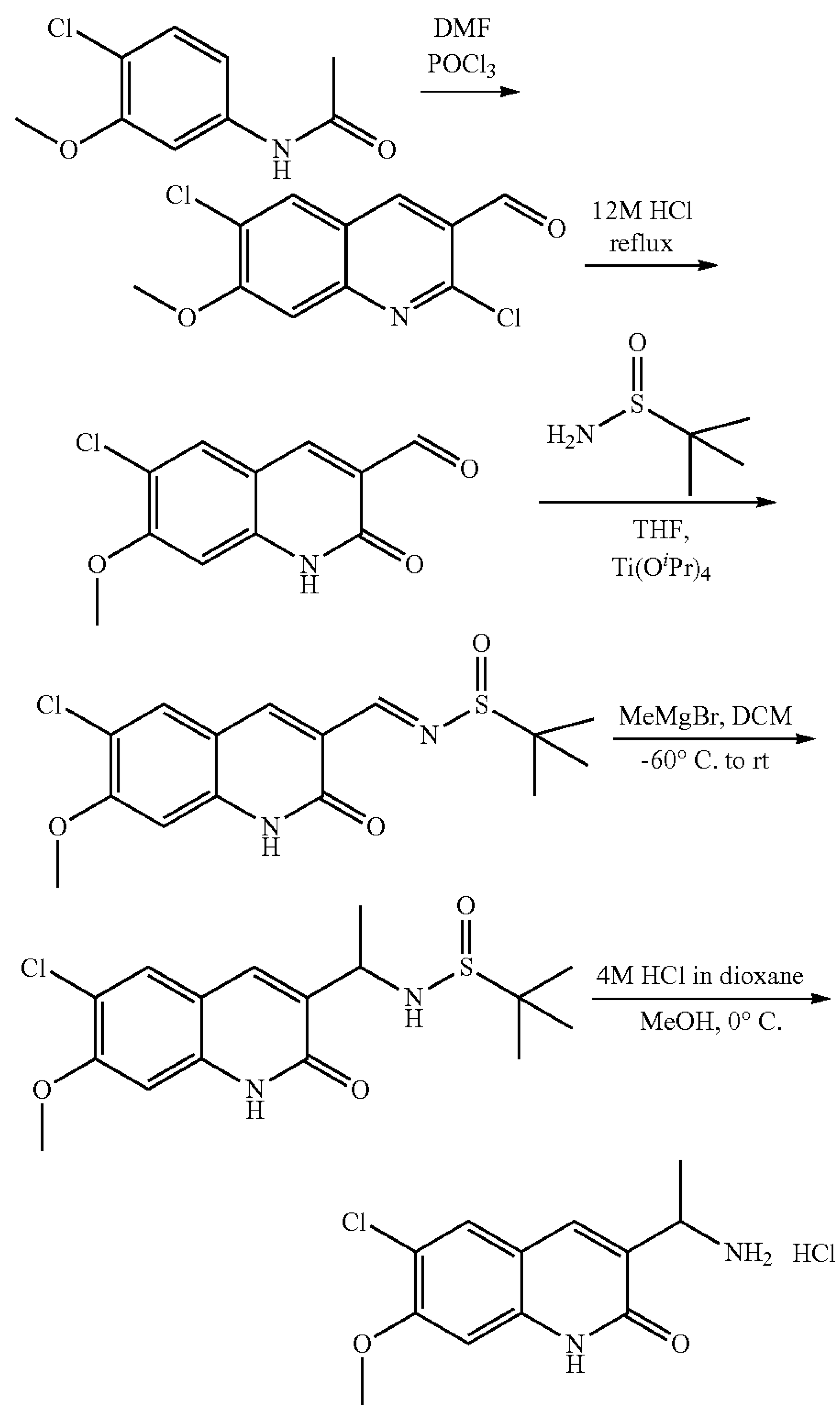
To a mixture of 3-acetyl-6-chloro-7-fluoroquinolin-2(1H)-one (6.4 g, 26.7 mmol) and (S)-2-methylpropane-2-sulfinamide (4.85 g, 40.06 mmol) in THF (450 mL) was added $Ti(OEt)_4$ (14 mL, 66.7 mmol). The resultant mixture was stirred at 80° C. overnight. Upon the completion of the reaction, the reaction mixture was cooled to −60° C. and $NaBH_4$ (5.1 g, 134 mmol) was added portion wise and then allowed to warm to room temperature overnight. The excess $NaBH_4$ was quenched with MeOH (20 mL), then with water (20 mL) and EtOAc (300 mL). The solution was filtered through a pad of celite. The filtrate was taken into a separatory funnel and the organic layer was separated, dried (Na_2SO_4), concentrated and purified by flash chromatography (SiO_2: hexanes/^{i}PrOH 0 to 20%) to give the title compound (4.5 g, 49%) as a yellow solid.

Step-6: (S)-3-(1-aminoethyl)-6-chloro-7-fluoroquinolin-2(1H)-one. HCl, II-3



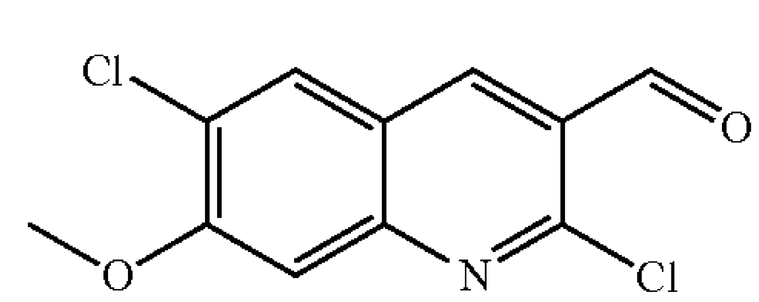
To a mixture of (S)—N—((S)-1-(6-chloro-7-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)-2-methyl propane-2-sulfinamide (3.5 g, 10.1 mmol) in MeOH (80 mL) was added 3N methanolic HCl (80 mL, 121 mmol). The resultant mixture was stirred at room temperature overnight. To this mixture was added diethyl ether (60 mL) and the resulting solid was filtered and dried to give the desired product II-3 (2.1 g, 75%) as a yellow solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.40 (br s, 1H), 8.24 (br s, 2H), 8.07-8.05 (m, 2H), 7.32 (d, J=10.4 Hz, 1H), 4.5-4.15 (m, 1H), 1.53 (d, J=6.8 Hz, 3H). LCMS (method LCMS3, APCI): Rt 3.47 min, m/z 241.1 [M+H]$^+$.

Example 6—Intermediate II-4: 3-(1-aminoethyl)-6-chloro-7-methoxyquinolin-2(1H)-one



II-4

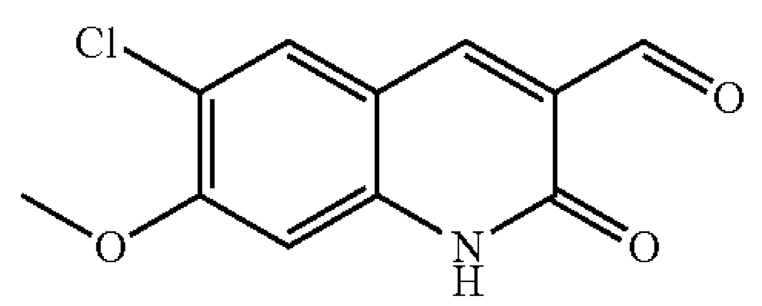
Step 1: 2,6-dichloro-7-methoxyquinoline-3-carbaldehyde



A tube was capped with a septum and placed under an atmosphere of nitrogen. DMF (6.4 mL, 83 mmol) was added by syringe and then cooled on an ice bath. $POCl_3$ (25 mL, 268 mmol) was added drop wise by syringe (over 20 minutes). The red solution was allowed to warm to room temperature (over 20 minutes), then the septum was removed, and the mixture was treated with N-(4-chloro-3-methoxyphenyl)acetamide (5 g, 25.05 mmol). The tube was sealed and the solution was stirred at 80° C. overnight. The solution was then pipetted onto ice, resulting in formation of a yellow precipitate. The precipitate was collected on a

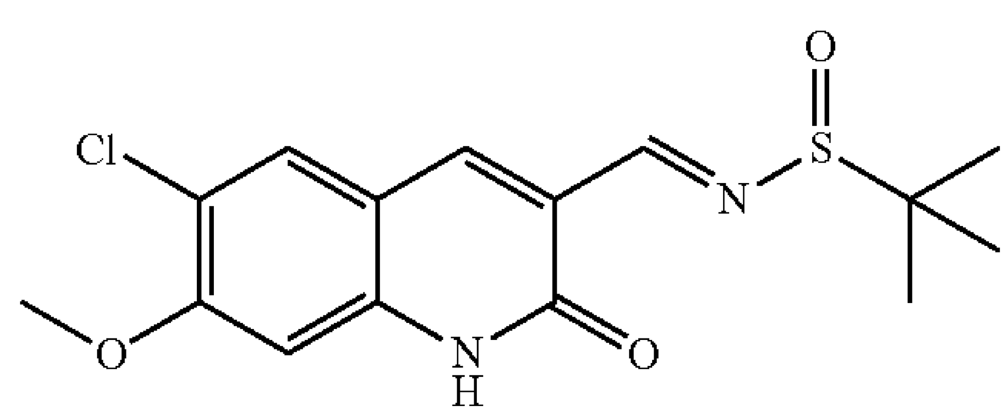
Buchner funnel, washed with water (1200 mL), and dried to provide 5.06 g of the title compound as a pale yellow solid. LCMS and [1]H NMR are consistent with 2,6-dichloro-7-methoxyquinoline-3-carbaldehyde (5.06 g, 19.76 mmol, 79% yield). [1]H NMR (300 MHz, DMSO-d_6): δ ppm 10.33 (s, 1H), 8.87 (s, 1H), 8.47 (s, 1H), 7.64 (s, 1H), 4.08 (s, 3H). LCMS (Method 1): m/z 256 $[M+H]^+$.

Step-2: 6-chloro-7-methoxy-2-oxo-1,2-dihydroquinoline-3-carbaldehyde



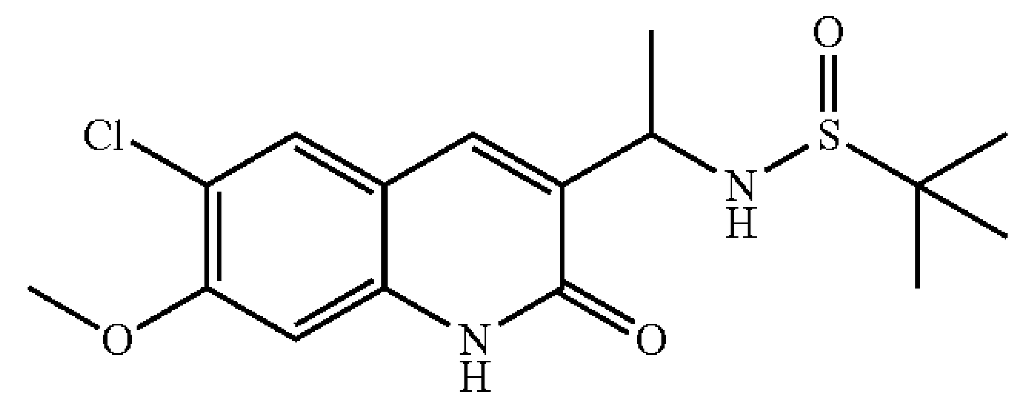
2,6-Dichloro-7-methoxyquinoline-3-carbaldehyde (5.06 g, 19.76 mmol) was heated at reflux in concentrated HCl (12M, 185 mL) overnight. The material went into solution during heating and then a solid precipitated during the course of the reaction. The mixture was allowed to cool and then was poured into water (1500 mL) resulting in further precipitation. The slurry was filtered on a Buchner funnel, washed with water (1500 mL), and dried to provide 4.04 g of the title compound as a yellowish-brown solid. LCMS and [1]H NMR are consistent with 6-chloro-7-methoxy-2-oxo-1,2-dihydroquinoline-3-carbaldehyde (4.04 g, 17.00 mmol, 86% yield). [1]H NMR (300 MHz, DMSO-d_6): δ ppm 12.22 (s, 1H), 10.16-10.18 (m, 1H), 8.43 (s, 1H), 8.08 (s, 1H), 6.95 (s, 1H), 3.94 (s, 3H). LCMS (Method 1): m/z 238 $[M+H]^+$.

Step-3: N-((6-chloro-7-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)methylene)-2-methyl propane-2-sulfinamide



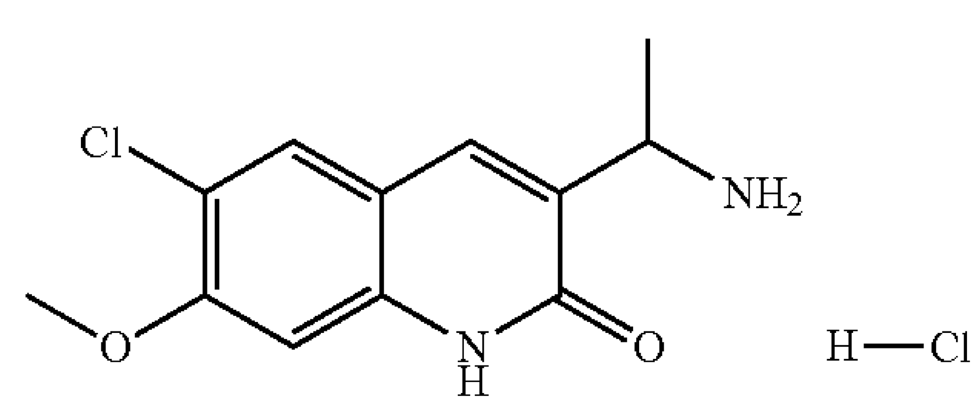
A mixture of 6-chloro-7-methoxy-2-oxo-1,2-dihydroquinoline-3-carbaldehyde (2.00 g, 8.42 mmol) and 2-methylpropane-2-sulfinamide (1.22 g, 10.07 mmol) was placed under an atmosphere of nitrogen. THF (20 mL) and titanium (IV) isopropoxide ($Ti(O^iPr)_4$) (5.0 mL, 17.06 mmol) were added by syringe and the resulting suspension was stirred at room temperature overnight. Once LCMS indicated the reaction had gone to completion, the reaction was quenched by drop wise addition of aqueous saturated NH_4Cl (10 mL). The mixture was triturated with EtOAc (450 mL), then filtered through Celite® 545, and the Celite® was washed further with EtOAc (200 mL). The filter cake was then sonicated in EtOAc (450 mL) for 15 minutes, then filtered on a Buchner funnel. The two filtrates were combined, washed with brine (200 mL), dried (Na_2SO_4), filtered, and evaporated under reduced pressure to provide 1.01 g of the title compound as a yellow solid. LCMS and [1]H NMR are consistent with (E)-N-((6-chloro-7-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)methylene)-2-methylpropane-2-sulfinamide (1.01 g, 2.96 mmol, 35.2% yield). [1]H NMR (300 MHz, DMSO-d_6): δ ppm 12.21 (s, 1H), 8.74 (s, 1H), 8.59 (s, 1H), 8.08 (s, 1H), 6.97 (s, 1H), 3.94 (s, 3H), 1.19 (s, 9H). LCMS (Method 1): m/z 341 $[M+H]^+$.

Step-4: N-(1-(6-chloro-7-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)-2-methylpropane-2-sulfinamide



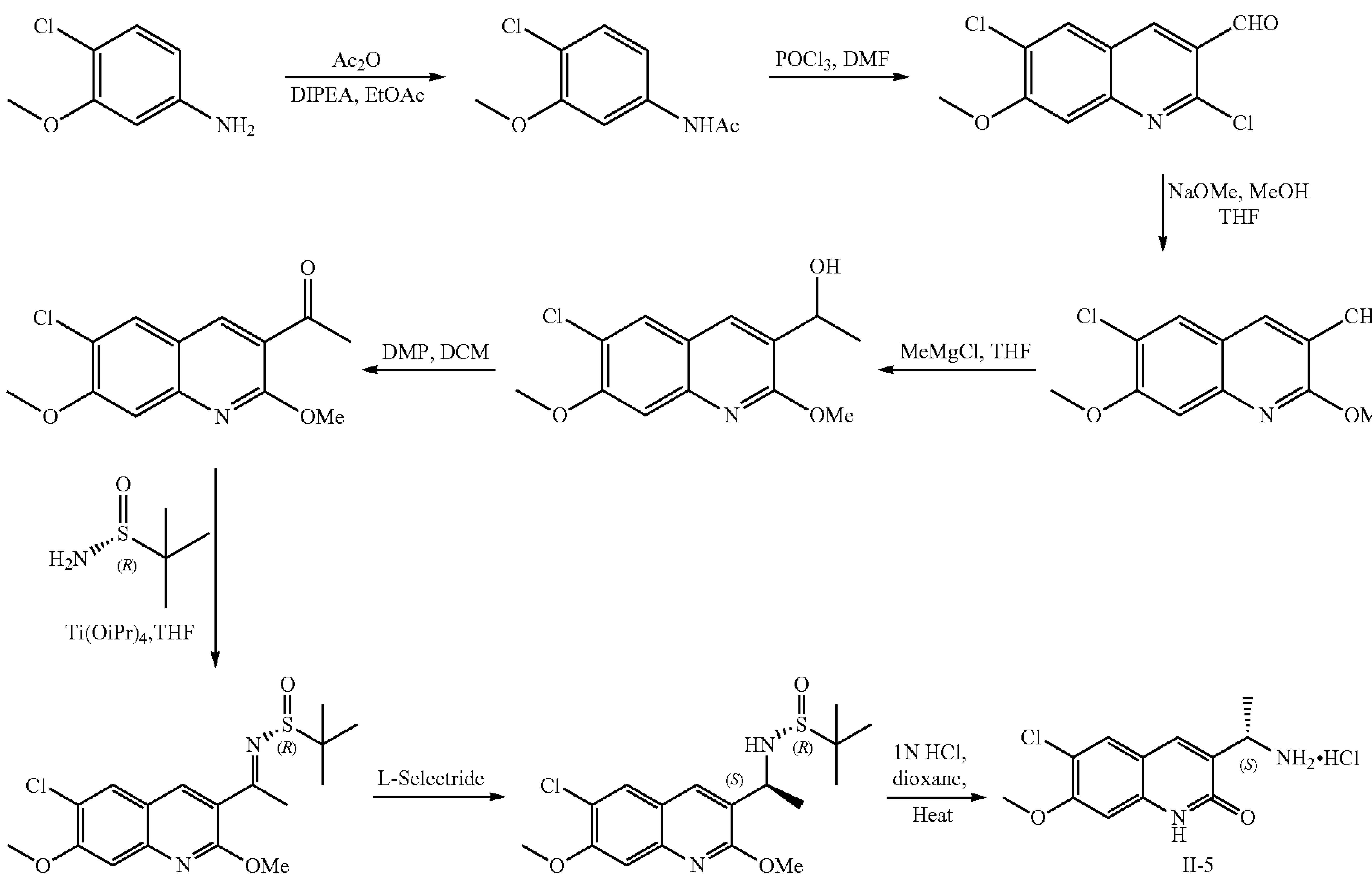
N-((6-chloro-7-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)methylene)-2-methylpropane-2-sulfinamide (265 mg, 0.778 mmol) was placed in a 50 mL round-bottom flask under an atmosphere of nitrogen. DCM (7 mL) was added, and the suspension was cooled on a dry ice/chloroform bath (to approx. −60° C.). Methylmagnesium bromide (MeMgBr) (3M in ether, 0.80 mL, 2.40 mmol) was added drop wise. The reaction mixture was stirred at −60° C. for several hours, then allowed to warm to room temperature overnight, resulting in an orange solution. Once LCMS indicated the reaction had gone to completion, the suspension was cooled on an ice bath and treated drop wise with water (3 mL). The resulting mixture was diluted with water (75 mL) and extracted with EtOAc (75 mL+20 mL). Silica gel was added and the EtOAc was evaporated under reduced pressure to provide a wet globular mass. Heptane and MeOH were added and the mixture was evaporated under reduced pressure to provide a powder. The material was purified by column chromatography on a Biotage® MPLC chromatography system (eluted with 0 to 4.2% MeOH in DCM) to yield the title compound as a blue-green brittle foam. LCMS and [1]H NMR are consistent with N-(1-(6-chloro-7-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)-2-methylpropane-2-sulfinamide (152.7 mg, 0.428 mmol, 55% yield). LCMS (Method 1): m/z 357 $[M+H]^+$.

Step-5: 3-(1-aminoethyl)-6-chloro-7-methoxyquinolin-2(1H)-one hydrochloride (II-4)

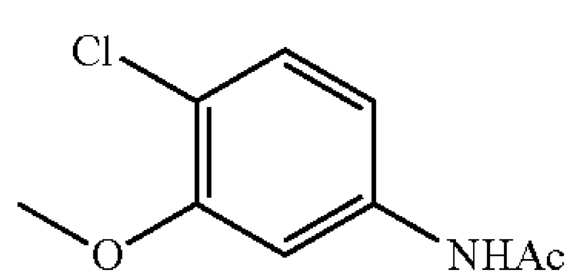


A solution of N-(1-(6-chloro-7-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)-2-methyl propane-2-sulfinamide (149.6 mg, 0.419 mmol) in MeOH (3.8 mL) was cooled on an ice bath and treated drop wise with 4M HCl in 1,4-dioxane (2.2 mL). The reaction was stirred for 25 minutes, during which time a small amount of precipitate formed. The solvents were evaporated under reduced pressure at room temperature. The residue was triturated with 10 mL of ethyl ether, then collected on a Hirsch funnel, and washed with more ethyl ether to provide 115.6 mg of the title compound as a pale green solid. LCMS and ^{1}H NMR are consistent with 3-(1-aminoethyl)-6-chloro-7-methoxyquinolin-2(1H)-one hydrochloride II-4 (115.6 mg, 0.400 mmol, 95% yield). ^{1}H NMR (300 MHz, Methanol-d_4): δ ppm 7.95 (s, 1H), 7.77 (s, 1H), 6.97 (s, 1H), 4.51 (q, J=6.84 Hz, 1H), 3.98 (s, 3H), 1.68 (d, J=7.04 Hz, 3H). LCMS (Method 1): m/z 253 [M+H]$^+$.

Example 7—Intermediate II-5: (S)-3-(1-amino-ethyl)-6-chloro-7-methoxyquinolin-2(1H)-one

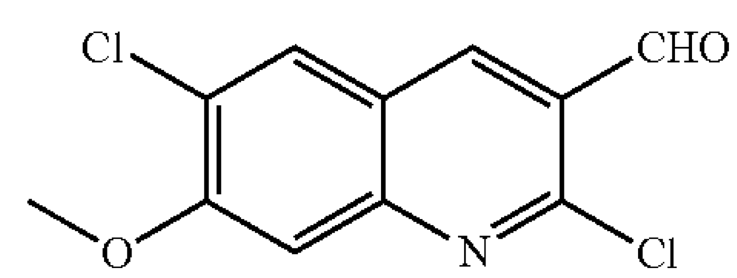


Step-1: N-(4-chloro-3-methoxyphenyl)acetamide



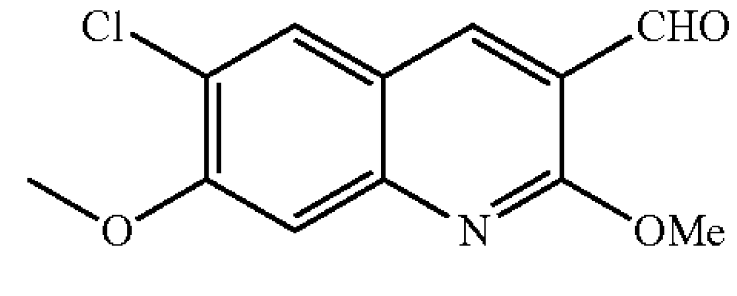
To a solution of 4-chloro-3-methoxyaniline (50 g, 317 mmol) and DIPEA (110 mL, 635 mmol) in CH_2Cl_2 (700 mL) was added acetic anhydride (36 mL, 381 mmol) drop wise at 0° C. and the reaction mixture was stirred at room temperature for 3 h. The reaction then was quenched with water (250 mL) and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (100 mL×3). The combined organic layers were dried (Na_2SO_4), concentrated and purified by flash chromatography with CH_2Cl_2/MeOH to give N-(4-chloro-3-methoxy phenyl)acetamide (71 g, quantitative yield) as a white solid.

Step-2: 2,6-Dichloro-7-methoxyquinoline-3-carbaldehyde



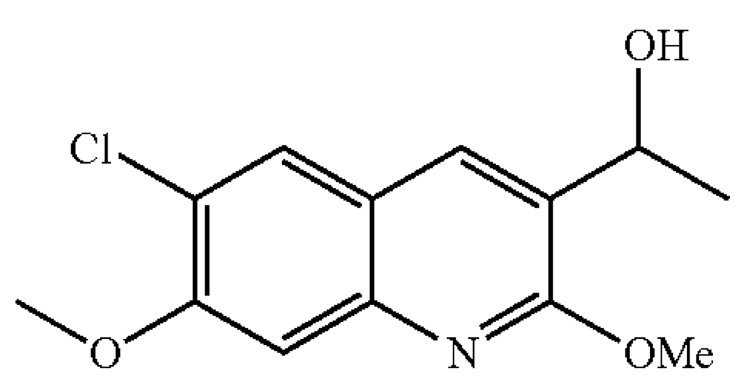
To $POCl_3$ (450 g, 274 mL, 2.95 mol) in a 2 L flask was added anhydrous DMF (83.5 g, 89 mL, 14 mol) drop wise. The reaction mixture was warmed up to room temperature and stirred for 20 min. After that N-(4-chloro-3-methoxy-phenyl)acetamide (65 g, 327 mmol) was added portion wise at room temperature and the mixture was heated to 90° C. overnight. The reaction mixture was then cooled to room temperature and carefully quenched into aqueous $NaHCO_3$ solution. The precipitation obtained was filtered, washed with water (100 mL×3) and then dried in vacuum oven to give 60 g of title compound (73%).

Step-3: 6-Chloro-2,7-dimethoxyquinoline-3-carbaldehyde



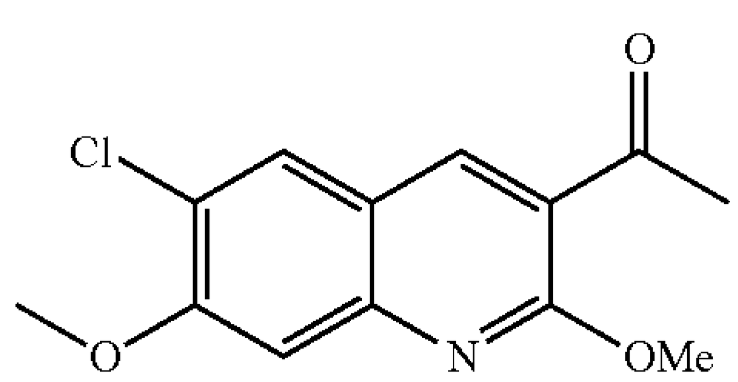
To 2,6-dichloro-7-methoxyquinoline-3-carbaldehyde (40 g, 157 mmol) in MeOH (1 L) and THF (200 mL) was added NaOMe (16.9 g, 314 mmol) portion wise at room temperature. The reaction mixture was refluxed for 3 h. After cooling to room temperature, the reaction was quenched by addition of aqueous NH_4Cl solution (200 mL). The mixture was extracted with EtOAc (200 mL×3). The combined organic layers were dried (Na_2SO_4), concentrated and purified by flash chromatography with hexanes/EtOAc (3:1) to give the desired product (37.89 g, 96%) as a yellow solid.

Step-4:
1-(6-chloro-2,7-dimethoxyquinolin-3-yl)ethanol



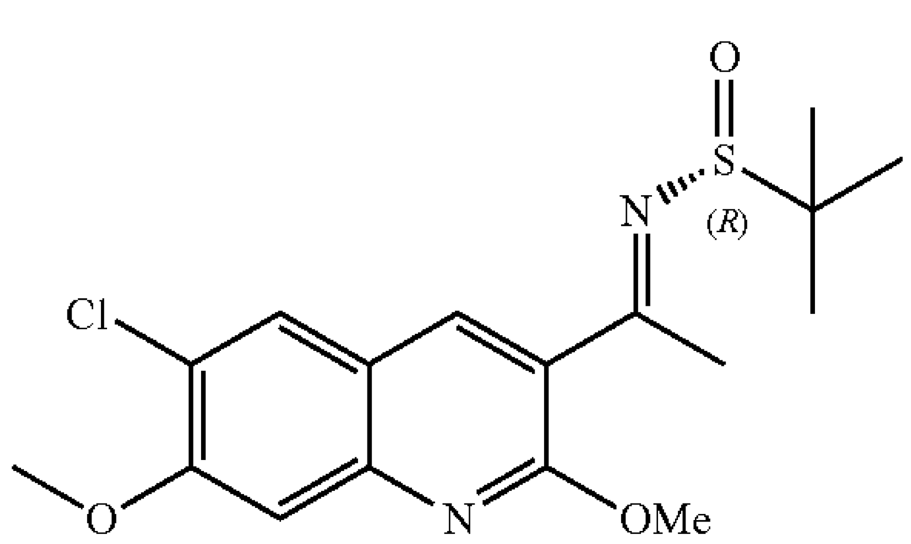
To a solution of 6-chloro-2,7-dimethoxyquinoline-3-carbaldehyde (36.74 g, 151 mmol) in THF (1 L) at −78° C. was added a solution of MeMgCl in THF (3 M, 75.5 mL, 226 mmol) drop wise. The reaction was stirred at room temperature for 3 h and then quenched with aqueous NH_4Cl solution (250 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (100 mL×3). The combined organic layers were dried (Na_2SO_4), concentrated, and purified by silica gel chromatography with hexanes/EtOAc (3:1) to afford the title compound (38.06 g, 91%).

Step-5:
1-(6-chloro-2,7-dimethoxyquinolin-3-yl)ethanone



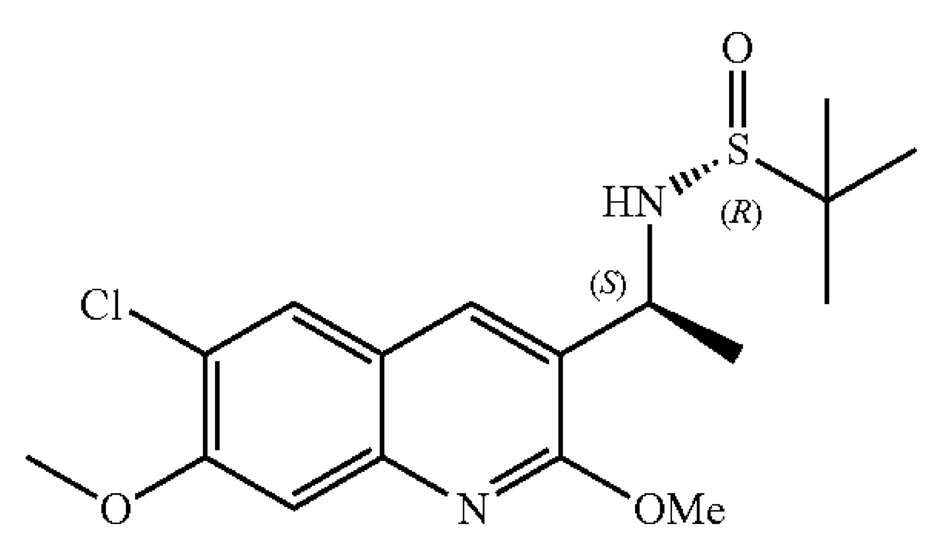
To 1-(6-chloro-2,7-dimethoxyquinolin-3-yl)ethanol (36.74 g, 137.6 mmol) in CH_2Cl_2 (1 L) at 0° C. was added DMP (70.0 g, 165.1 mmol) portion wise. The reaction was stirred at room temperature for 2 h, and then was quenched with an aqueous solution of $NaHCO_3$ and $Na_2S_2O_3$. After stirring for 15 min, both layers became clear. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (100 mL×2). The combined organic layers were dried (Na_2SO_4), concentrated and purified by silica gel chromatography with hexanes/EtOAc (4:1) to afford the title compound (30.02 g, 80%) as a white solid.

Step-6: (R,E)-N-(1-(6-chloro-2,7-dimethoxyquinolin-ethylidene)-2-methylpropane-2-sulfinamide



To 1-(6-chloro-2,7-dimethoxyquinolin-3-ethanone (30.07 g, 113.5 mmol) in THF/toluene (100 mL/1 L) at room temperature was added (R)-2-methylpropane-2-sulfinamide (27.5 g, 227 mmol) and $Ti(OiPr)_4$ (97 mL, 340.5 mmol,). The reaction was refluxed with a Dean-Stark apparatus. After the reaction was refluxed for 4 h and 300 mL of solvent was removed, the reaction was cooled to room temperature. The solvent was removed under vacuum, and 200 mL of EtOAc was added to the residue, followed by 100 mL of saturated aqueous $NaHCO_3$ solution. After stirring for 10 min, the reaction mixture was passed through a pad of celite. The filtrate was extracted with EtOAc (200 mL×2), dried (Na_2SO_4), concentrated and purified by silica gel chromatography with hexanes/EtOAc (1:1) to give the title compound (34.28 g, 82%).

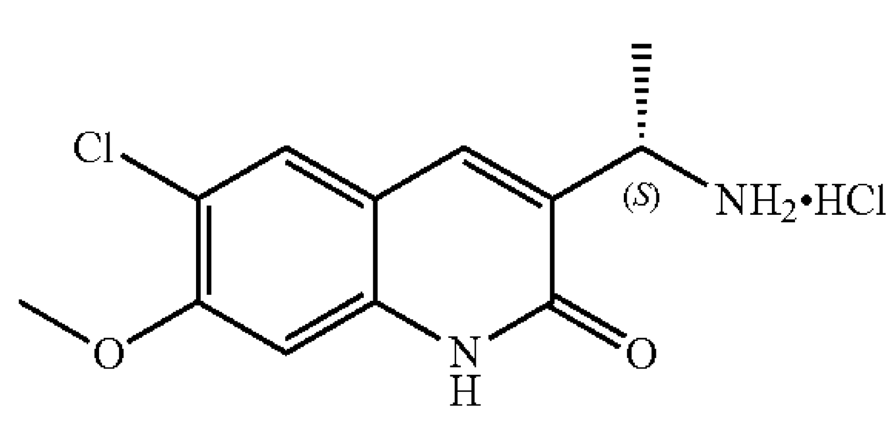
Step-7: (R)—N—((S)-1-(6-chloro-2,7-dimethoxyquinolin-3-yl)ethyl)-2-methylpropane-2-sulfinamide



To (R,E)-N-(1-(6-chloro-2,7-dimethoxyquinolin-3-yl)ethylidene)-2-methylpropane-2-sulfinamide (34.28 g, 93.15 mmol) in THF (600 mL) at −78° C., was added 1 M L-selectride (121 mL, 121 mmol) in THF drop wise. The reaction mixture was warmed to room temperature and stirred for 3 h. The reaction was quenched with aqueous saturated NH_4Cl (300 mL) solution and then extracted with EtOAc (200 mL×2). The combined organic layers were dried (Na_2SO_4), concentrated and purified by silica gel chromatography with hexanes/EtOAc (1:1) to afford the title compound (29.27 g, 85%).

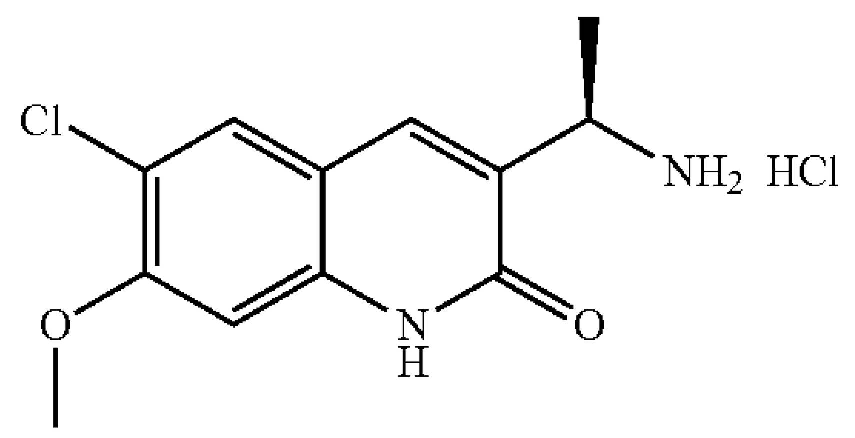
Step-8: (S)-3-(1-aminoethyl)-6-chloro-7-methoxyquinolin-2(1H)-one hydrochloride salt (II-5)

II-5



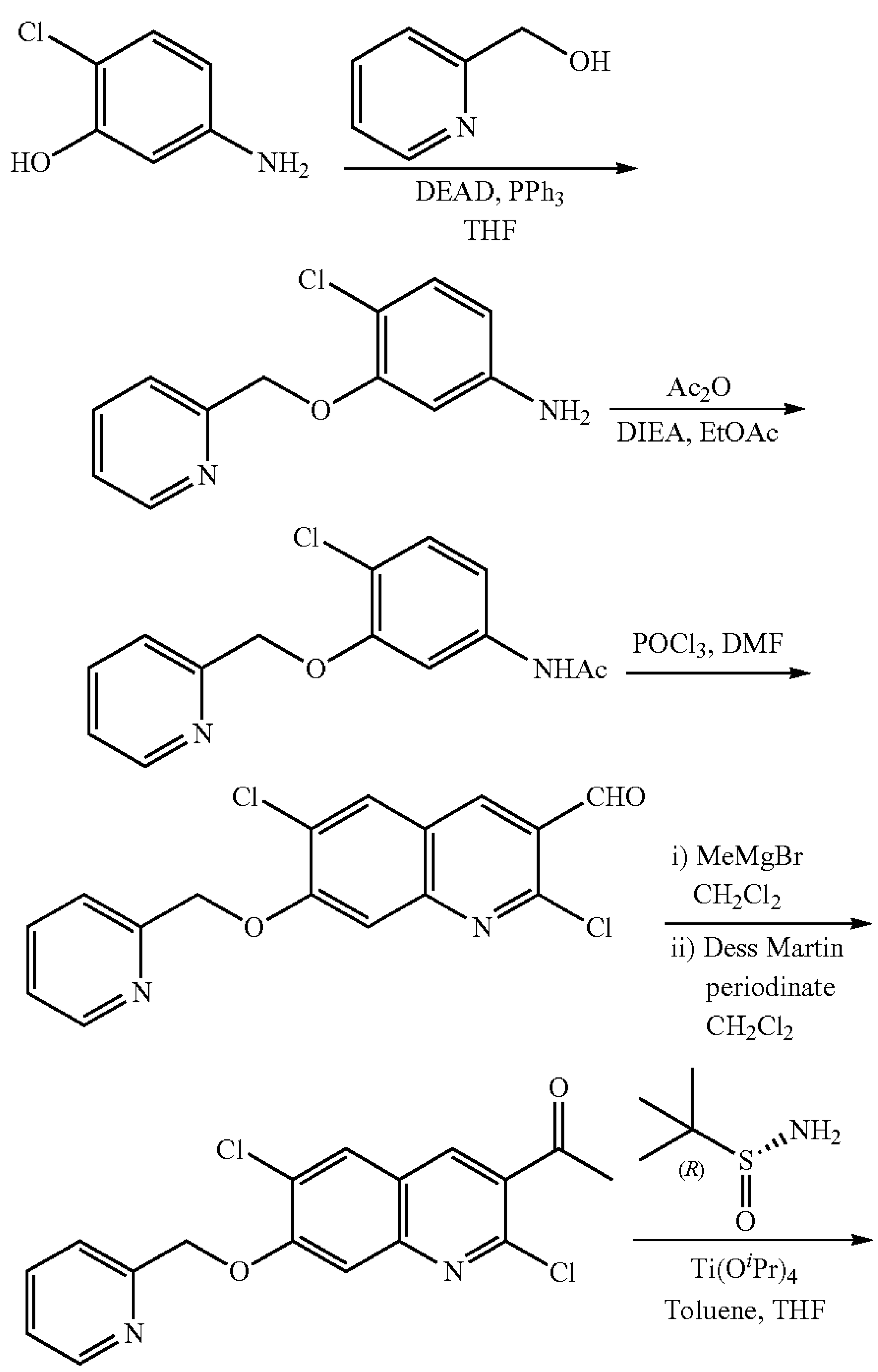
To (R)—N—((S)-1-(6-chloro-2,7-dimethoxyquinolin-3-yl)ethyl)-2-methylpropane-2-sulfinamide (30.35 g, 82 mmol) in dioxane (250 mL) was added 2 N HCl (250 mL) at rt. The reaction mixture was refluxed for 3 h, cooled to room temperature and the solvent was removed under vacuum. The crude residue obtained was dried under vacuum to give a crude product, which was further purified by trituration (CH_2Cl_2/MeOH/hexane) to obtain pure title compound II-5 (17.65 g, 75%) as a white solid. ^1H NMR (300 MHz, DMSO-d6): δ 12.18 (s, 1H), 8.24 (br, s, 3H), 7.99 (s, 1H), 7.86 (s, 1H), 7.02 (s, 1H), 4.41 (m, 1H), 3.91 (s, 3H), 1.52 (d, J=6.87 Hz, 3H). LCMS (Method 3): Rt 3.48 min, m/z 253.1 [M+H]$^+$.

Example 8—Intermediate II-6: (R)-3-(1-amino-ethyl)-6-chloro-7-methoxyquinolin-2(1H)-one



The title compound II-6 was prepared in the same procedure described for II-5, except using (S)-2-methylpropane-2-sulfinamide in Step-6 (Scheme-3). ^{1}H NMR (300 MHz, Methanol-d$_4$): δ ppm 7.92 (s, 1H), 7.75 (s, 1H), 6.95 (s, 1H), 4.48 (q, J=6.84 Hz, 1H), 3.96 (s, 3H), 1.65 (d, J=6.74 Hz, 3H). LCMS: m/z 253 [M+H]$^+$.

Example 9—Intermediate II-7: (S)-3-(1-amino-ethyl)-6-chloro-7-(pyridin-2-ylmethoxy) quinolin-2(1H)-one



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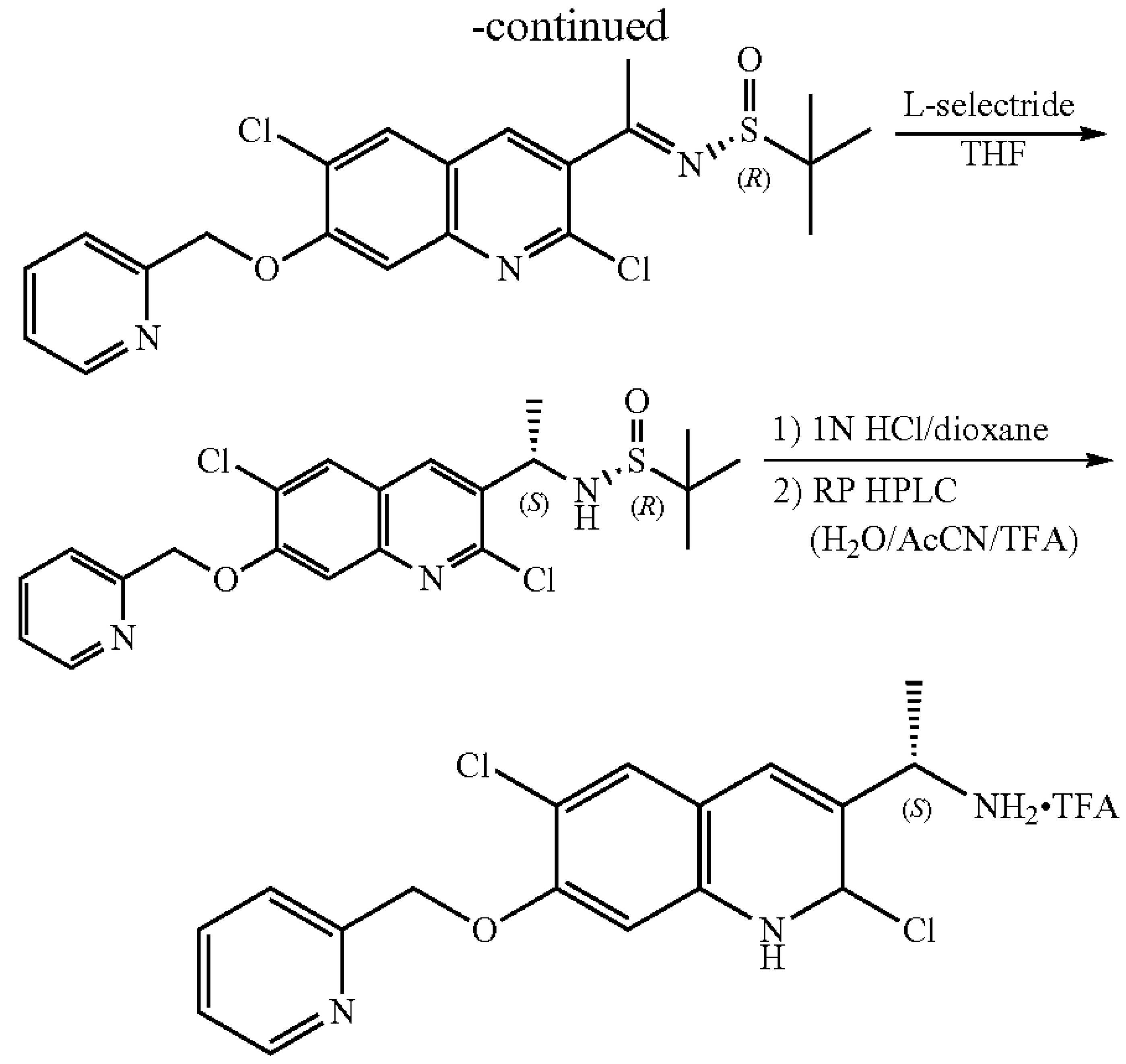
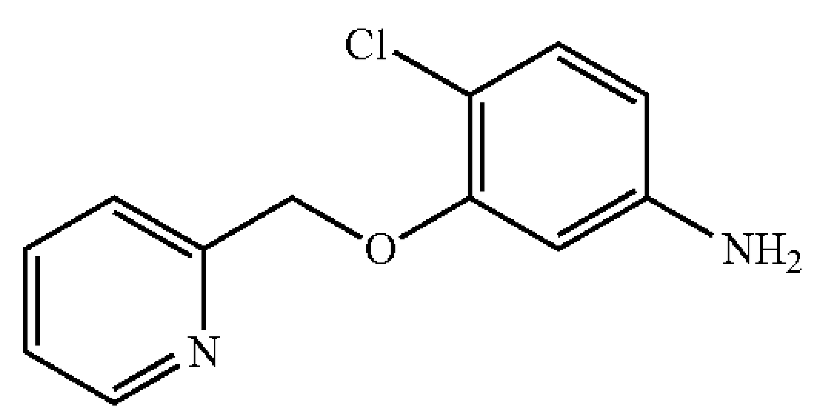


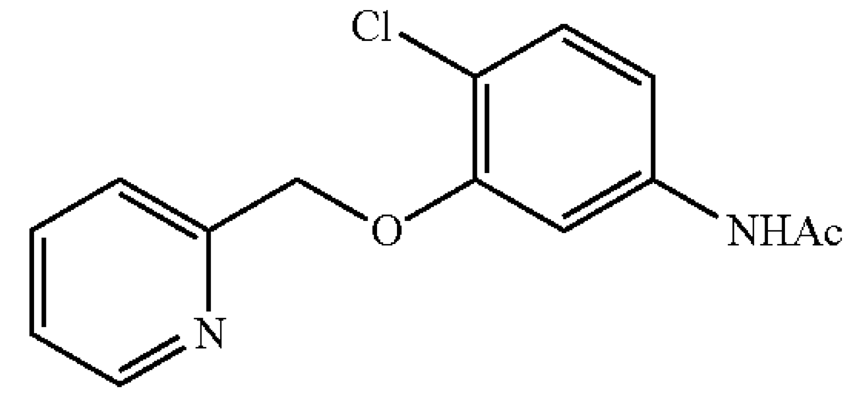
II-7

Step-1: 4-Chloro-3-(pyridin-2-ylmethoxy)aniline



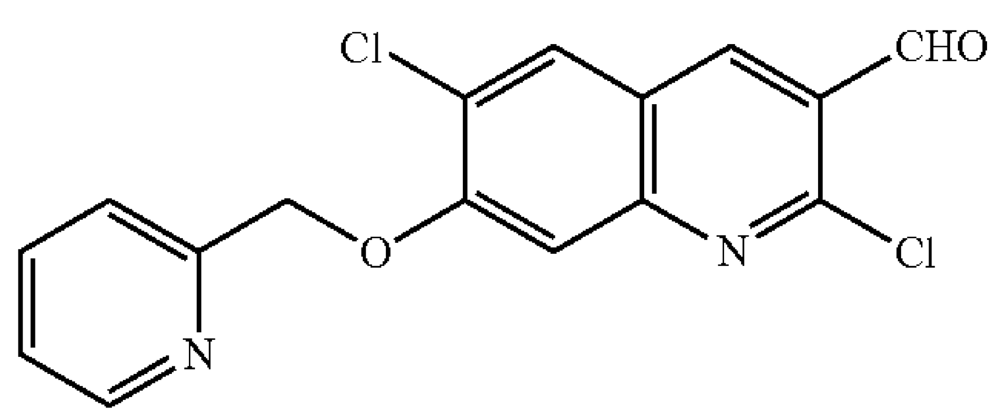
To a mixture of 5-amino-2-chlorophenol (10 g, 69.63 mmol), pyridin-2-ylmethanol (7.98 g, 73.13 mmol) and triphenylphosphine (21.5 g, 82.07 mmol) in THF (1.1 L) was added slowly diethylazadicarboxylate (DEAD) (13 mL, 82.07 mmol) at room temperature. The resulting mixture was stirred at room temperature for 24 hours. Upon completion of reaction, SiO_2 was added and solvents were evaporated to dryness. The crude product was purified by SiO_2 column chromatography eluted with 0-100% EtOAc-hexanes and then with 2% MeOH in EtOAc to afford the title compound (11.8 g, 72%) as an off-white solid. Note: The ^{1}H NMR showed a small amount of triphenylphosphine oxide impurity. This material was used in the next step without further purification.

Step-2: N-(4-Chloro-3-(pyridin-2-ylmethoxy)phenyl)acetamide



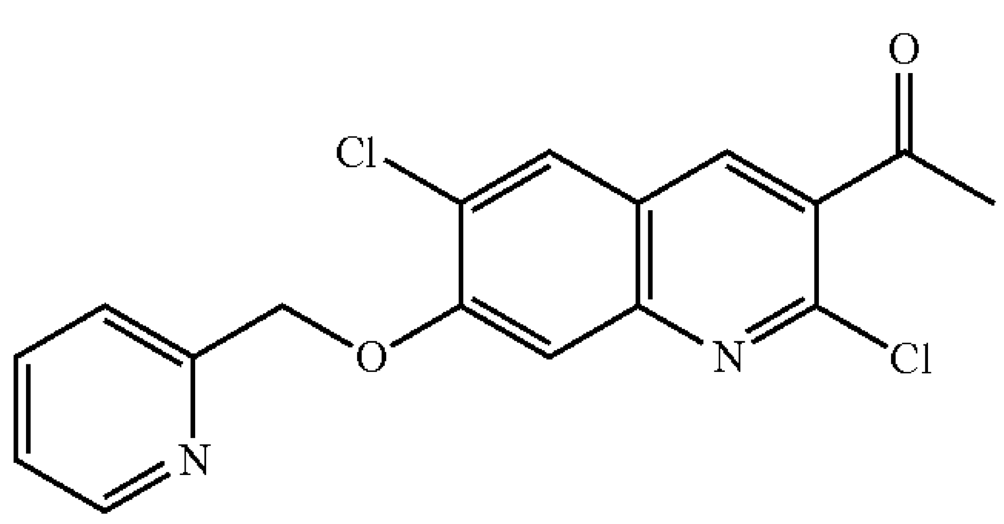
To a mixture of 4-chloro-3-(pyridin-2-ylmethoxy)aniline (11.8 g, 50.27 mmol) and diisopropylethylamine (DIEA) (9.93 mL, 57.81 mmol) in ethyl acetate (250 mL) was added acetic anhydride (Ac_2O) (5.22 mL, 55.3 mmol). The resultant mixture was stirred overnight at ambient temperature. The mixture was diluted with EtOAc (1 L), and washed with water (200 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and evaporated to dryness. The resulting residue was triturated with hexanes-dichloromethane to afford the title compound as white solid (11.62 g, 84% yield).

Step-3: 2,6-Dichloro-7-(pyridin-2-ylmethoxy)quinoline-3-carbaldehyde



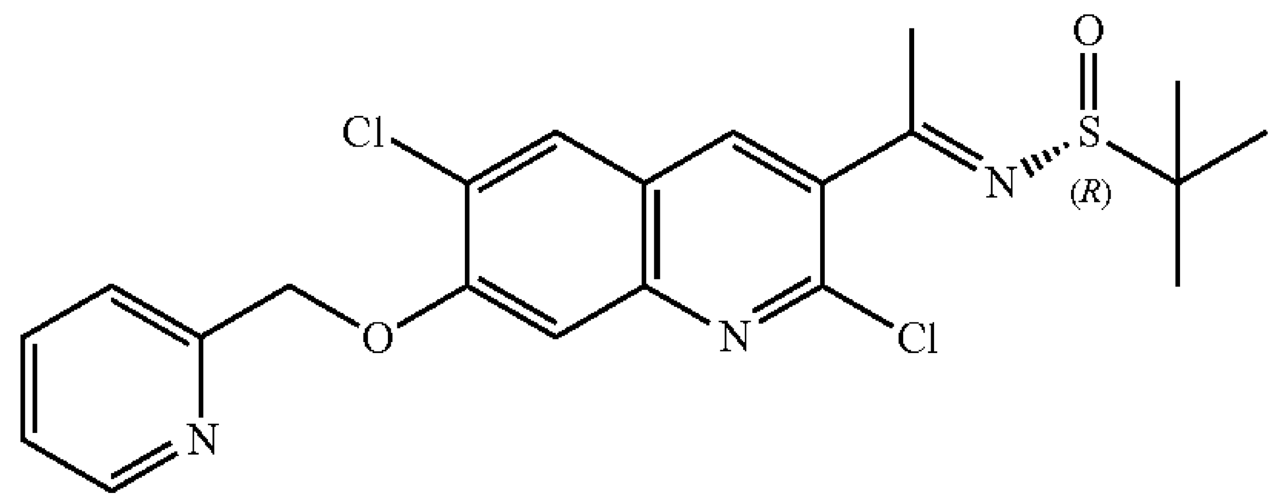
Dimethylformamide (4 mL, 51.6 mmol) was placed in a 150 mL sealed tube and cooled to 0° C. To the DMF was added phosphorous oxychloride ($POCl_3$) (15.6 mL, 168 mmol) drop wise over 30-40 minutes. The resulting mixture was warmed to room temperature and N-(4-chloro-3-(pyridin-2-ylmethoxy)phenyl)acetamide (4.34 g, 15.68 mmol) was added. The reaction mixture was heated at 80° C. overnight. The mixture was then cooled to room temperature and carefully quenched with ice. The solution turned red and a yellow precipitate was formed, filtered, washed with water and dried over P_2O_5 overnight to afford the title compound as yellow solid (3.53 g, 68% yield).

Step-4: 1-(2,6-Dichloro-7-(pyridin-2-ylmethoxy)quinolin-3-yl)ethanone



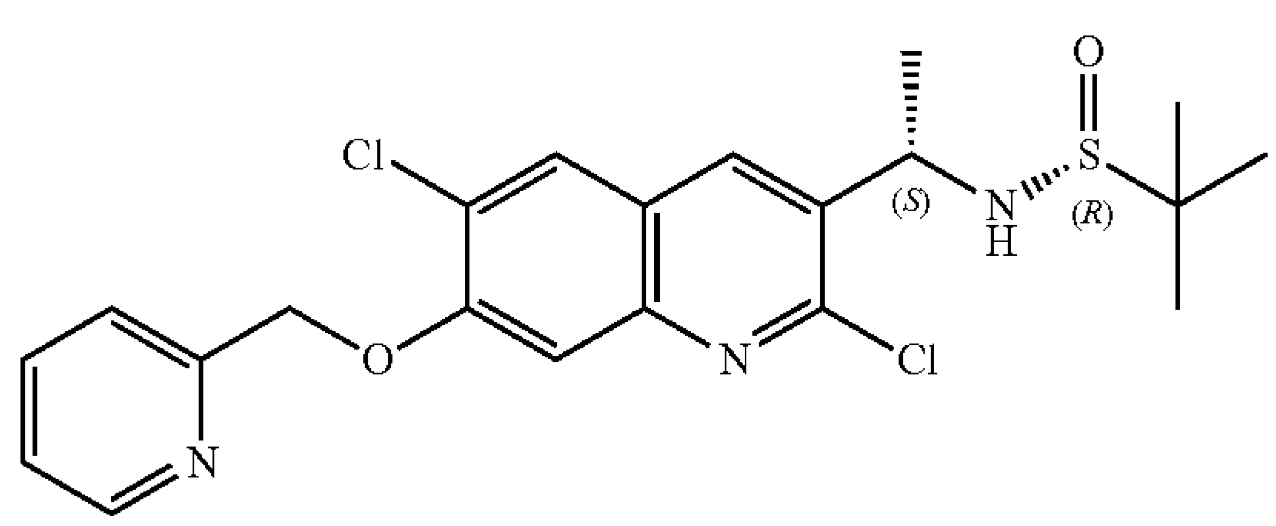
To a solution of 2,6-dichloro-7-(pyridin-2-ylmethoxy)quinoline-3-carbaldehyde (1.0 g, 3.0 mmol) in CH_2Cl_2 (40 mL) was added drop wise methyl magnesium bromide (MeMgBr) (3 M solution in diethyl ether, 1.5 mL, 4.50 mmol) at 0° C. The resulting mixture was then stirred at ambient temperature for 1.5 hours. Upon completion of reaction, the mixture was slowly quenched with water mL) and extracted with CH_2Cl_2 (50 mL). The organic layer was separated and dried over anhydrous Na_2SO_4. The solvents were evaporated to dryness. The resulting residue was dissolved in CH_2Cl_2 (25 mL) and treated with Dess-Martin Periodinate (2.54 g, 6.00 mmol). The mixture was stirred at ambient temperature overnight. The mixture was then quenched with an aqueous co-solution of 20% $NaHCO_3$ and 20% $Na_2S_2O_3$ (10 mL) and stirred for 5 minutes at room temperature. The solution was extracted with CH_2Cl_2 (40 mL), dried over anhydrous Na_2SO_4, filtered and evaporated. The resulting residue was purified by column chromatography on an ISCO® chromatography system (SiO_2 column: eluted with CH_2Cl_2/MeOH 0 to 10%) to afford the title compound (800 mg, 79%).

Step-5: (R,E)-N-(1-(2,6-dichloro-7-(pyridin-2-ylmethoxy)quinolin-3-yl)ethylidene)-2-methylpropane-2-sulfinamide



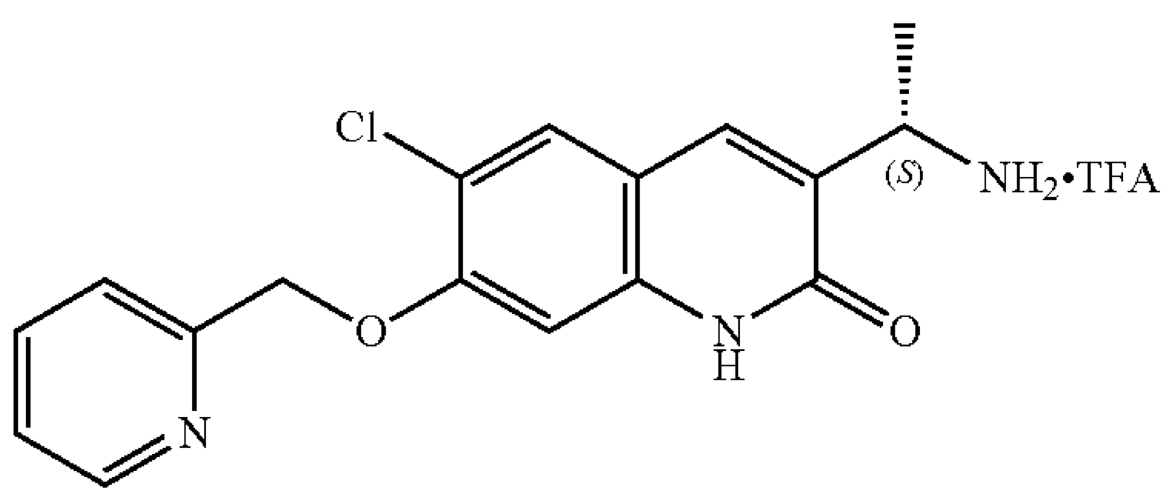
To a mixture of 1-(2,6-dichloro-7-(pyridin-2-ylmethoxy)quinolin-3-yl)ethanone (2.18 g, 6.56 mmol) and (R)-2-methylpropane-2-sulfinamide (1.19 g, 9.84 mmol) in THF: Toluene (40 mL:180 mL), was added titanium (IV) isopropoxide ($Ti(O^iPr)_4$) (3.96 mL, 13.30 mmol). The resulting mixture was refluxed with a Dean-Stark apparatus for 7 hours. The mixture was then cooled to room temperature, quenched with water, and diluted with EtOAc (300 mL). The organic layer was washed with water (100 mL), dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The resulting residue was purified by column chromatography on an ISCO® chromatography system (SiO_2 column: eluted with Hex/EtOAc 0 to 100%) to afford the title compound as yellow solid (1.4 g, 50% yield). The starting material ketone was also recovered (250 mg, 11% yield).

Step-6: (R)—N—((S)-1-(2,6-dichloro-7-(pyridin-2-ylmethoxy)quinolin-3-yl)ethyl)-2-methyl propane-2-sulfinamide



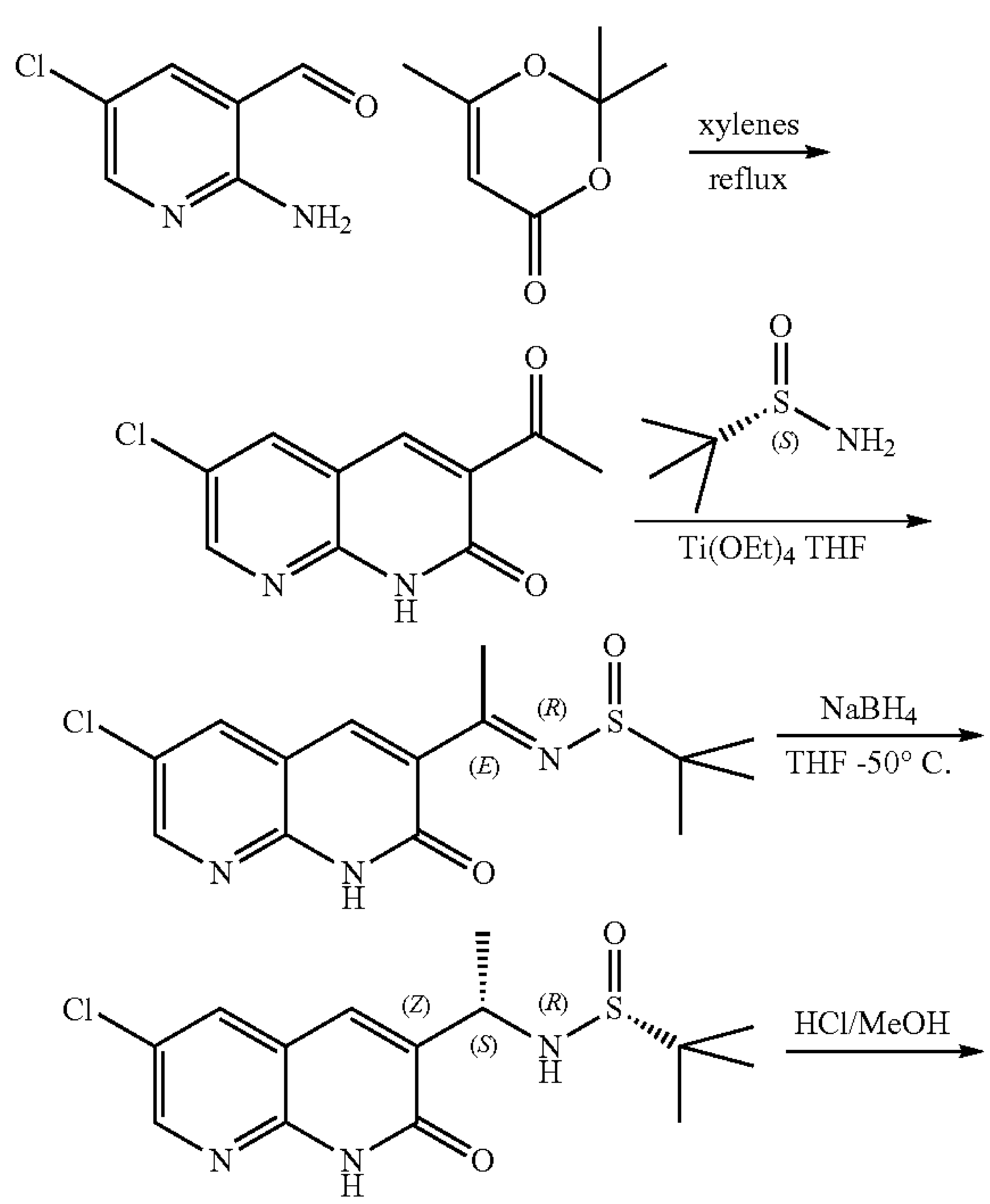
To a solution of (R,E)-N-(1-(2,6-dichloro-7-(pyridin-2-ylmethoxy)quinolin-3-yl) ethylidene)-2-methyl propane-2-sulfinamide (900 mg, 1.99 mmol) in THF (25 mL) at −40 to −50° C. was added L-selectride (1M in THF, 1.98 mL, 2.59 mmol) drop wise. The resulting mixture was stirred at −40 to −50° C. for 2 hours. Upon completion of reaction, the mixture was quenched with ice at −50° C., extracted with EtOAc (100 mL), dried, and evaporated. The resulting residue was purified by column chromatography on an ISCO® chromatography system (SiO_2 column: Hex/EtOAc 0 to 100%) followed by trituration with hexanes-methylene chloride to afford the title compound (266 mg, 30% yield).

Step-7: (S)-3-(1-Aminoethyl)-6-chloro-7-(pyridin-2-ylmethoxy)quinolin-2(1H)-one TFA salt (II-7)



To a mixture of (R)—N—((S)-1-(2,6-dichloro-7-(pyridin-2-ylmethoxy)quinolin-3-yl)ethyl)-2-methylpropane-2-sulfinamide (1.1 g, 2.43 mmol) in 1,4-dioxane (6.6 mL), was added aqueous 1N HCl (6.6 mL) at room temperature. The resulting mixture was heated to 120° C. overnight. After TLC and MS showed completion of reaction, the solvents were removed on a rotary evaporator and lyophilized to provide yellow solid. The crude solid was purified by reverse phase chromatography on an ISCO chromatography system (C18 column: eluted with H_2O/MeCN/0.1% CF_3CO_2H 0 to 100%) and the fractions were monitored by LCMS. The pure fractions were combined and lyophilized to afford the title compound II-7 (920 mg, 86% yield) as the TFA salt. ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.17 (br s, 1H), 8.62 (d, J=4.95 Hz, 1H), 8.09 (br s, 2H), 7.96-7.85 (m, 3H), 7.59 (d, J=7.9 Hz, 1H), 7.42-7.37 (m, 1H), 7.08 (d, J=2.5 Hz, 1H), 5.33 (s, 2H), 4.39-4.38 (m, 1H), 1.51 (d, J=6.8 Hz, 3H). LCMS (method 3): Rt 3.3 min, m/z 329.1 $[M+H]^+$.

Example 10—Intermediate II-8: (S)-3-(1-amino-ethyl)-6-chloro-1,8-naphthyridin-2(1H)-one



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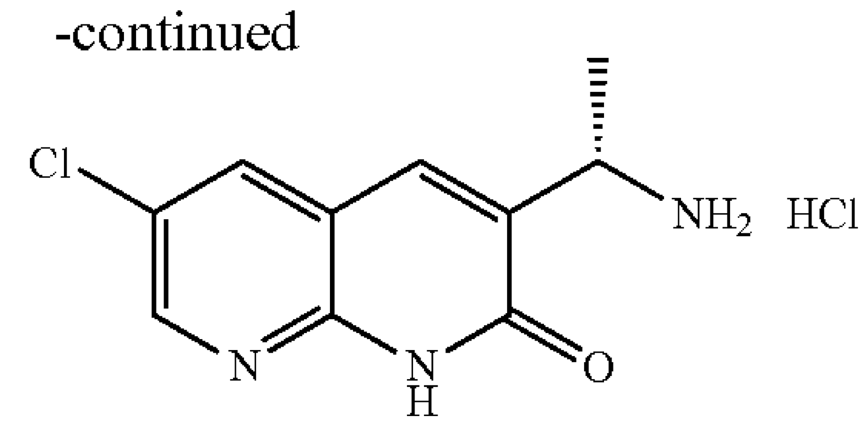
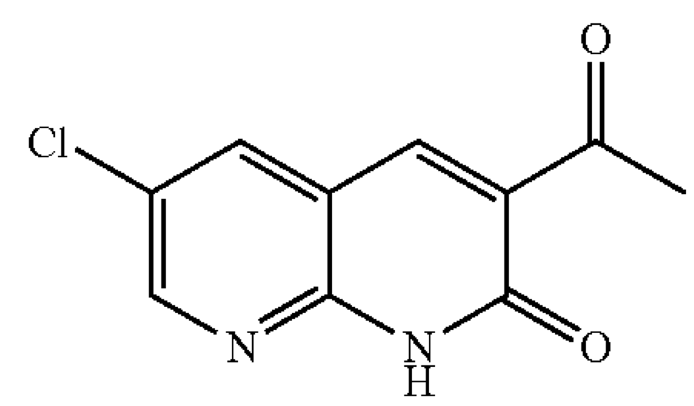


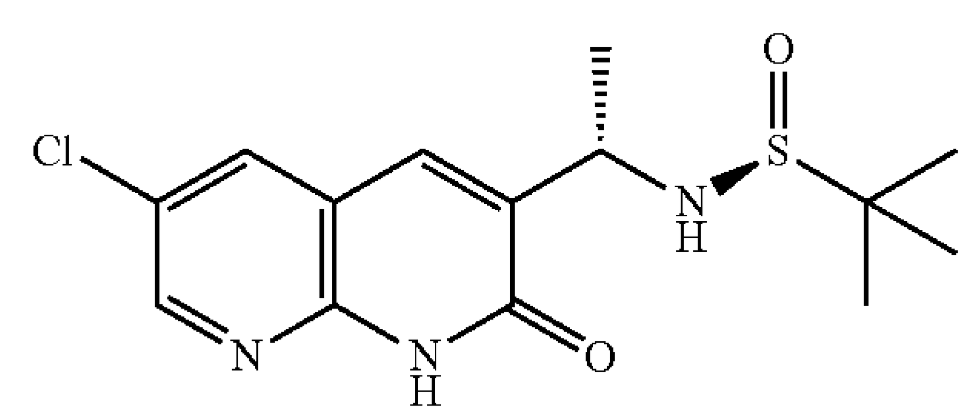
II-8

Step-1: 3-acetyl-6-chloro-1,8-naphthyridin-2(1H)-one



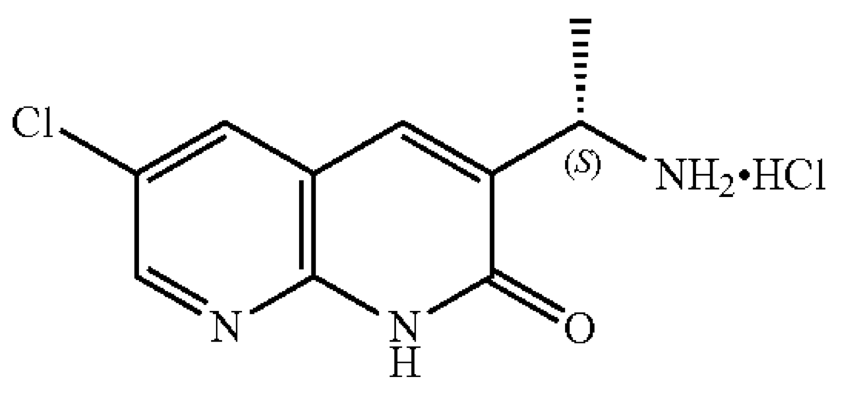
A mixture of 2-amino-5-chloronicotinaldehyde (1 g, 6.39 mmol) and 2,2,6-trimethyl-4H-1,3-dioxin-4-one (1.362 g, 9.58 mmol) in xylenes (10 mL) was heated to reflux for 3 hours, then cooled to room temperature, filtered, and washed with xylenes twice to afford 914 mg of 3-acetyl-6-chloro-1,8-naphthyridin-2(1H)-one (64.3% yield). ^{1}H NMR (300 MHz, DMSO-d_6): δ 12.68 (br, 1H), 8.63 (s, 1H), 8.49 (s, 1H), 8.39 (s, 1H), 2.48 (s, 3H). LCMS (Method 1): Rt 1.60 min, m/z 223.03$[M+H]^+$.

Step-2: (S)—N—((S)-1-(2,6-dichloroquinolin-3-yl) ethyl)-2-methylpropane-2-sulfinamide



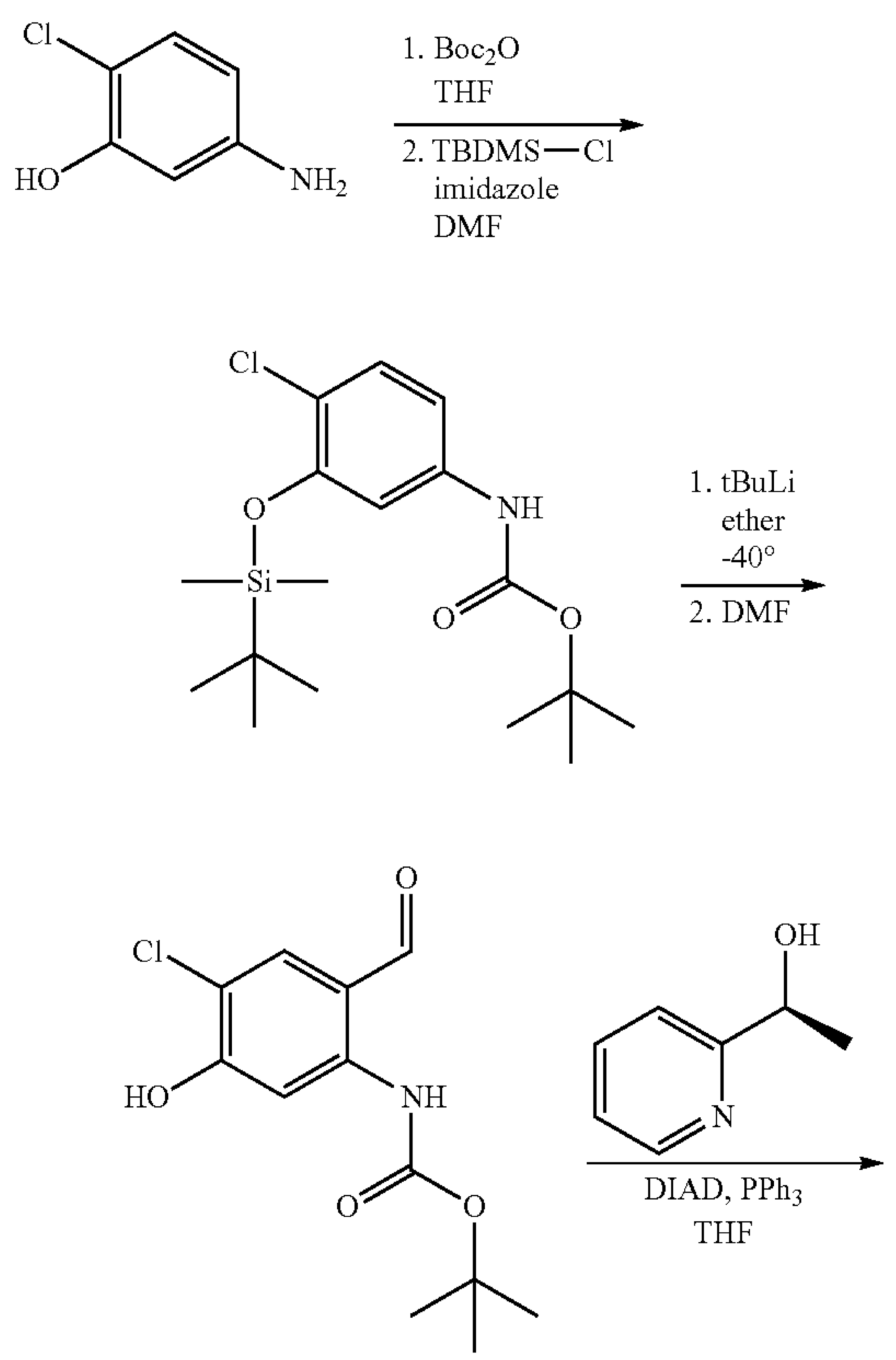
A mixture of tetraethoxytitanium (512 mg, 2.25 mmol), (R)-2-methylpropane-2-sulfinamide (163 mg, 1.35 mmol) and 3-acetyl-6-chloro-1,8-naphthyridin-2(1H)-one (200 mg, 0.898 mmol) in THF (15 mL) was heated to 80° C. overnight, then cooled to room temperature. To this mixture was added $NaBH_4$ (170 mg, 4.49 mmol) and the mixture was slowly warmed up to room temperature overnight. MeOH was then added to quench any excess $NaBH_4$, followed by the addition of water. The mixture was filtered to remove solids, then extracted with EtOAc twice, dried over Na_2SO_4, and concentrated. The residue was purified on a Biotage® chromatography system using a 25 g SiO_2 column eluted on a gradient (first 20% to 100% EtOAc/Hexanes, then 0-5% MeOH/DCM) to afford (S)—N—((S)-1-(2,6-dichloroquinolin-3-yl)ethyl)-2-methylpropane-2-sulfinamide (123 mg, 42% yield). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.40 (s, 1H), 7.74 (s, 1H), 7.75 (s, 1H), 7.24 (s, 1H), 5.24 (d, J=9.45 Hz, 1H), 4.42 (m, 3H), 1.54 (d, J=6.93 Hz, 3H), 1.20 (s, 9H). LCMS (Method 1): Rt 2.07 min, m/z 328.98 $[M+H]^+$.

Step-3: (S)-3-(1-aminoethyl)-6-chloro-1,8-naphthyridin-2(1H)-one (II-8)



To a solution of ((S)—N—((S)-1-(6-chloro-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl)ethyl)-2-methylpropane-2-sulfinamide (123 mg, 0.375 mmol) in MeOH (5 mL) was added HCl (2 mL, 8.00 mmol, 4M in 1,4-dioxane). The mixture was then stirred at room temperature overnight. To this mixture was added 6 mL of ethyl ether and the resulting precipitate was filtered, washed with ethyl ether (2×), dried and concentrated to afford (5)-3-(1-aminoethyl)-6-chloro-1,8-naphthyridin-2(1H)-one, HCl (96 mg, 98% yield). ^{1}H NMR (300 MHz, DMSO-d$_6$): δ 12.75 (br s, 1H), 8.60-8.35 (s, 1H), 8.26 (br, 1H) 8.07 (s, 1H), 4.40-4.50 (m, 1H), 1.51 (d, J=6.78 Hz, 3H). LCMS (Method 1): Rt 0.87 min, m/z 224.99 [M+H]$^{+}$.

Example 11—Intermediate II-9: (3-((S)-1-aminoethyl)-6-chloro-7-(pyridin-2-yl)ethoxy)quinolin-2(1H)-one



J

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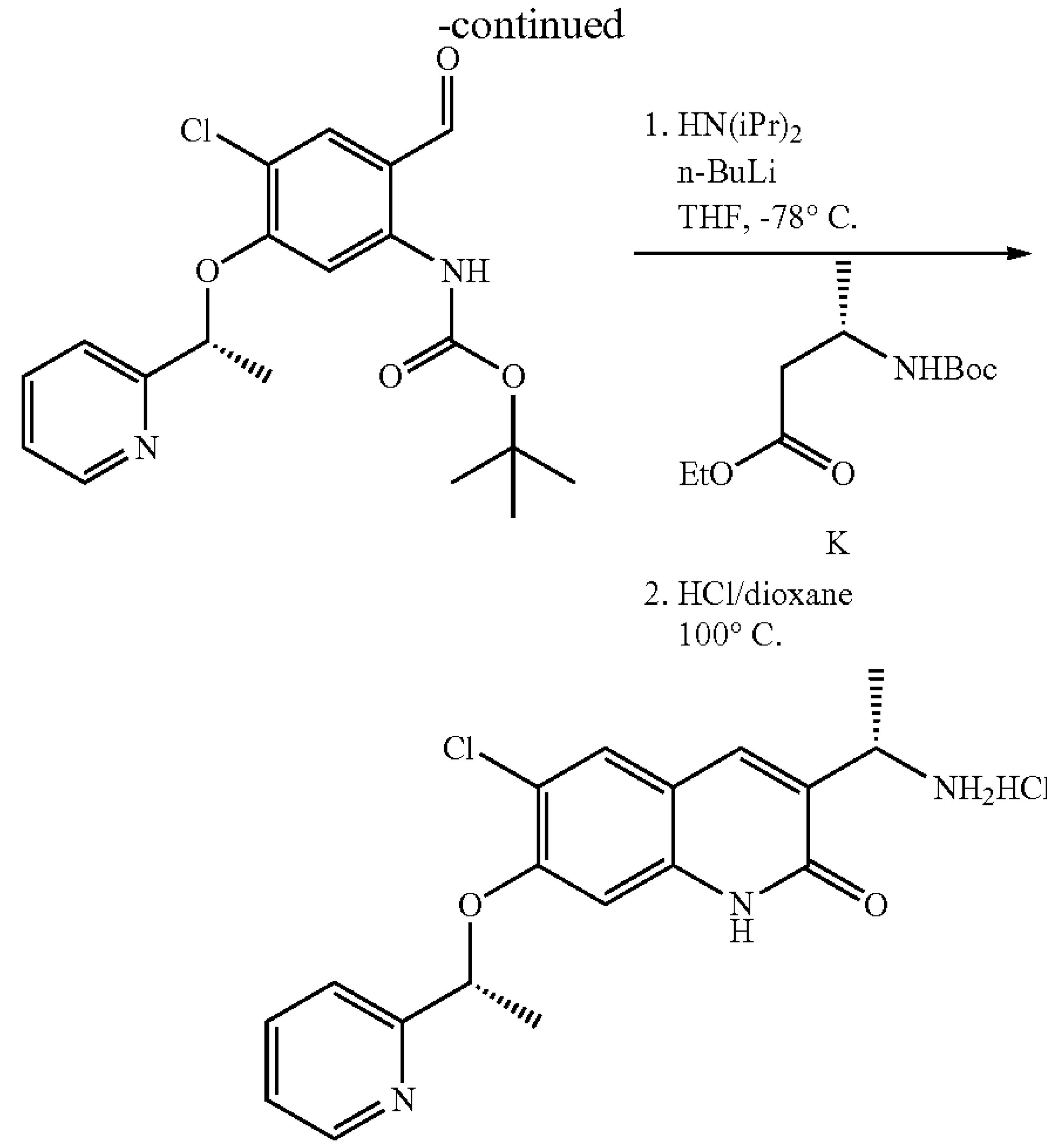
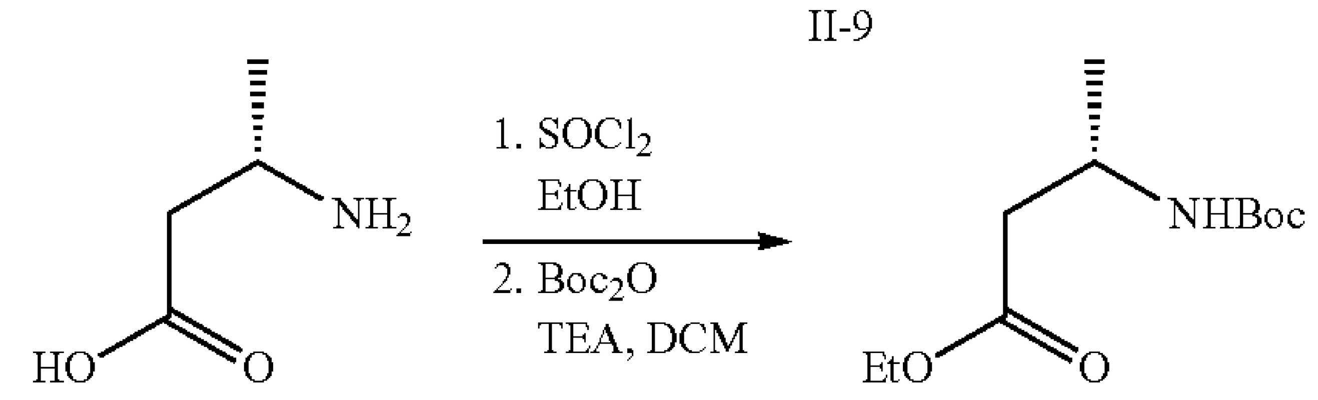
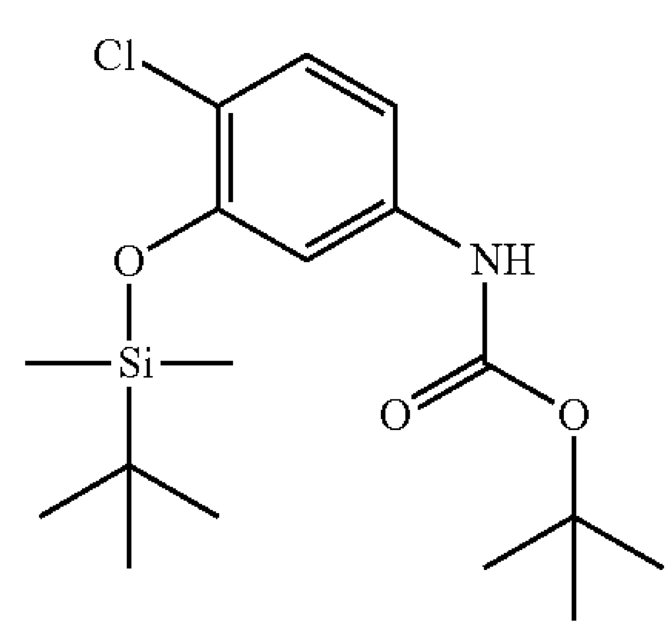


II-9



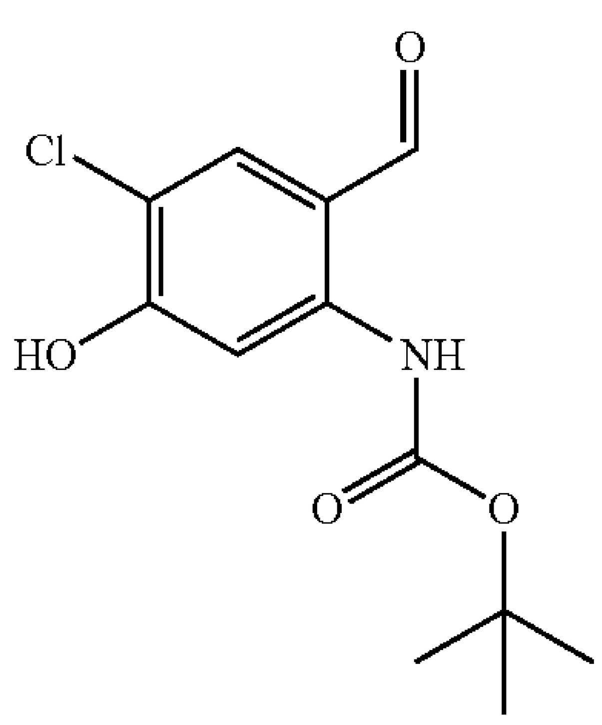
K

Step-1: tert-butyl (3-((tert-butyldimethylsilyl)oxy)-4-chlorophenyl)carbamate



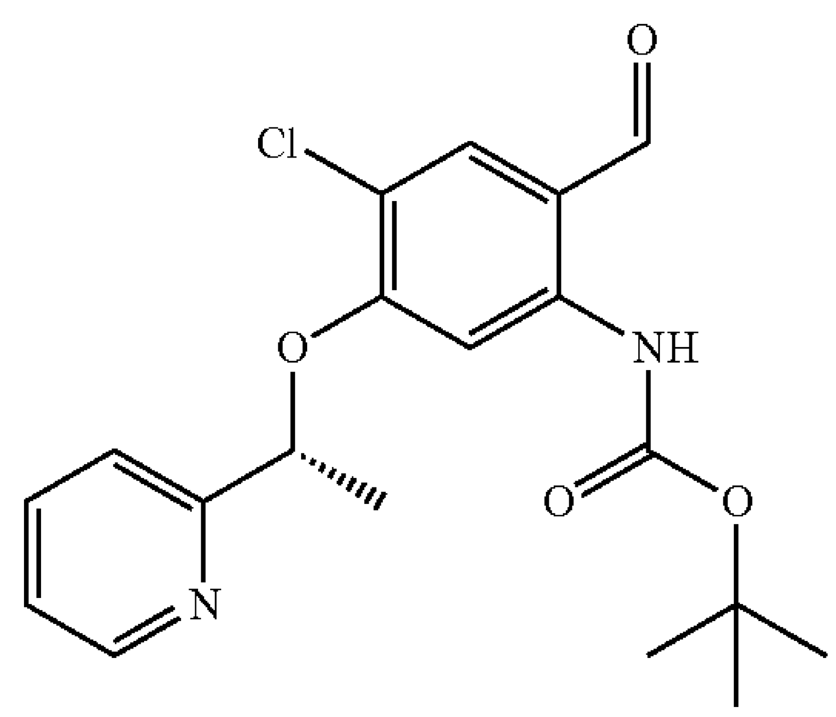
A solution of 5-amino-2-chlorophenol (10.00 g, 69.7 mmol) in THF (350 mL) was treated with di-tert-butyl dicarbonate (20 mL, 86 mmol) and stirred at reflux overnight. The solvent was evaporated under reduced pressure to provide a brown oil. The oil was then dissolved in EtOAc (300 mL), washed with water, saturated aqueous $NaHCO_3$, and brine (300 mL each), dried (Na_2SO_4), filtered, and evaporated under reduced pressure to provide 21.01 g of impure tert-butyl (4-chloro-3-hydroxyphenyl)carbamate as a brown oil (LCMS: m/z 244 [M+H]$^{+}$). This material was dissolved in DMF (130 mL) and cooled on an ice bath. Imidazole (11.74 g, 172 mmol) was then added slowly (over ~10 minutes). A solution of TBDMS-Cl (14.98 g, 99 mmol) in DMF (45 mL) was added (over ~2 minutes). The ice bath was removed and the solution was stirred at room temperature overnight. Once LCMS indicated the reaction had gone to completion, the solution was diluted with EtOAc (1 L) and washed with water (2×600 mL), half-saturated aqueous $NaHCO_3$ (600 mL), half-saturated aqueous NH_4Cl (600 mL), saturated $NaHCO_3$ (600 mL), and brine (600 mL). The organic layer was dried ($MgSO_4$), filtered, and evaporated under reduced pressure to provide 28.00 g of a brown solid. The sample was dissolved in EtOAc, silica gel (33 g) was added, and the solvent was evaporated under reduced pressure. The material was divided into two batches, each of which was purified by column chromatography on a Biotage® MPLC chromatography system using a 330 g silica gel column eluted with 0 to 5% EtOAc in hexanes and with isocratic elution at 4.5% or 5% EtOAc when the product eluted. The product fractions were collected and provided 21.76 g of tert-butyl (3-((tert-butyldimethylsilyl)oxy)-4-chlorophenyl)carbamate (21.76 g, 60.8 mmol, 88% yield) as a peach-colored solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ ppm 9.43 (s, 1H), 7.23-7.28 (m, 1H), 7.22 (d, J=2.35 Hz, 1H), 7.09-7.16 (m, 1H), 1.46 (s, 9H), 0.99 (s, 9H), 0.21 (s, 6H). LCMS (Method 1): m/z 358 $[M+H]^+$.

Step-2: tert-butyl (4-chloro-2-formyl-5-hydroxyphenyl)carbamate (J)



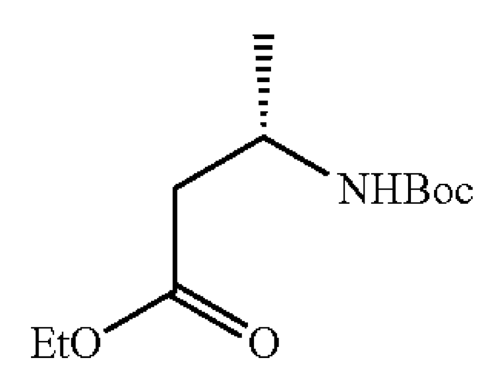
An oven-dried 3-necked 500 mL round bottom flask was charged with tert-butyl (3-((tert-butyldimethylsilyl)oxy)-4-chlorophenyl)carbamate (10 g, 27.9 mmol). An oven-dried addition funnel was attached, and the system was flushed with nitrogen. Ethyl ether (113 mL) was added by syringe. The resulting yellow solution was cooled on an acetonitrile/dry ice bath (to approximately −40° C.). t-BuLi (1.7 M in pentane, 40 mL, 68.0 mmol) was then added to the addition funnel by cannula. The t-BuLi solution was added dropwise to the ether solution (over ~10 minutes), during which time the ether solution gradually became cloudy with a precipitate. The mixture was stirred at about −40° C. for 2.5 hours, and then DMF (11 mL) was added dropwise by syringe (over ~10 minutes), during which time the solids went back into solution. The acetonitrile/dry ice bath was replaced with an ice bath, and the yellow solution was stirred at 0° C. for 1.75 hours. The reaction was then quenched by dropwise addition of water (25 mL), resulting in formation of an orange precipitate. The ice bath was removed and the sample was diluted with water (125 mL), resulting in dissolution of the precipitate. The mixture was shaken, and the layers were separated. The aqueous layer was acidified to pH 4-5 with AcOH. The resulting precipitate was extracted with EtOAc (200 mL), washed with water (2×100 mL), dried (Na_2SO_4), filtered, and evaporated under reduced pressure to provide tert-butyl (4-chloro-2-formyl-5-hydroxyphenyl)carbamate as a yellow solid (4.79 g, 17.63 mmol, 63% yield). ^{1}H NMR (300 MHz, DMSO-d_6): δ ppm 11.72 (s, 1H), 10.50 (s, 1H), 9.68 (br s, 1H), 7.99 (s, 1H), 7.88-7.91 (m, 1H), 1.48 (s, 9H). LCMS (Method 1): m/z 216 (M-56, loss of t-Bu).

Step-3: (R)-tert-butyl (4-chloro-2-formyl-5-(1-(pyridin-2-yl)ethoxy)phenyl)carbamate



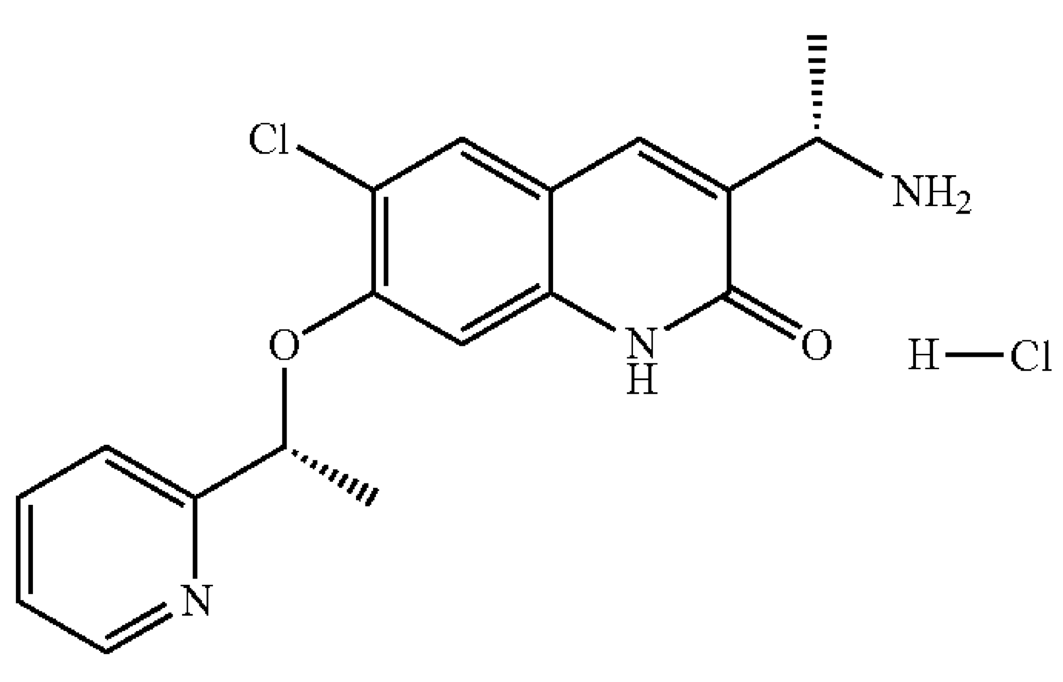
A mixture of (S)-1-(pyridin-2-yl)ethanol (454.3 mg, 3.69 mmol) 136C755F, tert-butyl (4-chloro-2-formyl-5-hydroxyphenyl)carbamate (1 g, 3.68 mmol) and triphenylphosphine (1.158 g, 4.42 mmol) was placed in a 100 mL round bottom flask under an atmosphere of nitrogen. THF (40 mL) was added by syringe. The resulting yellow solution was cooled on an ice bath and then DIAD (0.86 mL, 4.42 mmol) was added dropwise. The ice bath was removed and the solution was stirred at room temperature overnight. Once LCMS indicated the reaction had gone to completion, silica gel was added and the solvent was evaporated under reduced pressure. The sample was purified by column chromatography on a Biotage® MPLC chromatography system (using a 50 g silica gel column eluted with 0 to 13% EtOAc in hexanes) to provide 473.7 mg of a white solid. LCMS and NMR are consistent with (R)-tert-butyl (4-chloro-2-formyl-5-(1-(pyridin-2-yl)ethoxy)phenyl)carbamate contaminated with phenolic starting material (~5:1 product to starting material by NMR). The material was used for next step without further purification. ^{1}H NMR (300 MHz, DMSO-d_6): δ ppm 10.42 (s, 1H), 9.73 (s, 1H), 8.54-8.60 (m, 1H), 7.98 (s, 1H), 7.92 (s, 1H), 7.82 (ddd, J=7.80, 7.80, 1.80 Hz, 1H), 7.44 (br d, J=7.90 Hz, 1H), 7.30-7.36 (m, 1H), 5.64 (q, J=6.35 Hz, 1H), 1.67 (d, J=6.45 Hz, 3H), 1.46 (s, 9H). LCMS (Method 1): m/z 377 $[M+H]^+$.

Step-4: (S)-ethyl 3-((tert-butoxycarbonyl)amino) butanoate (K)



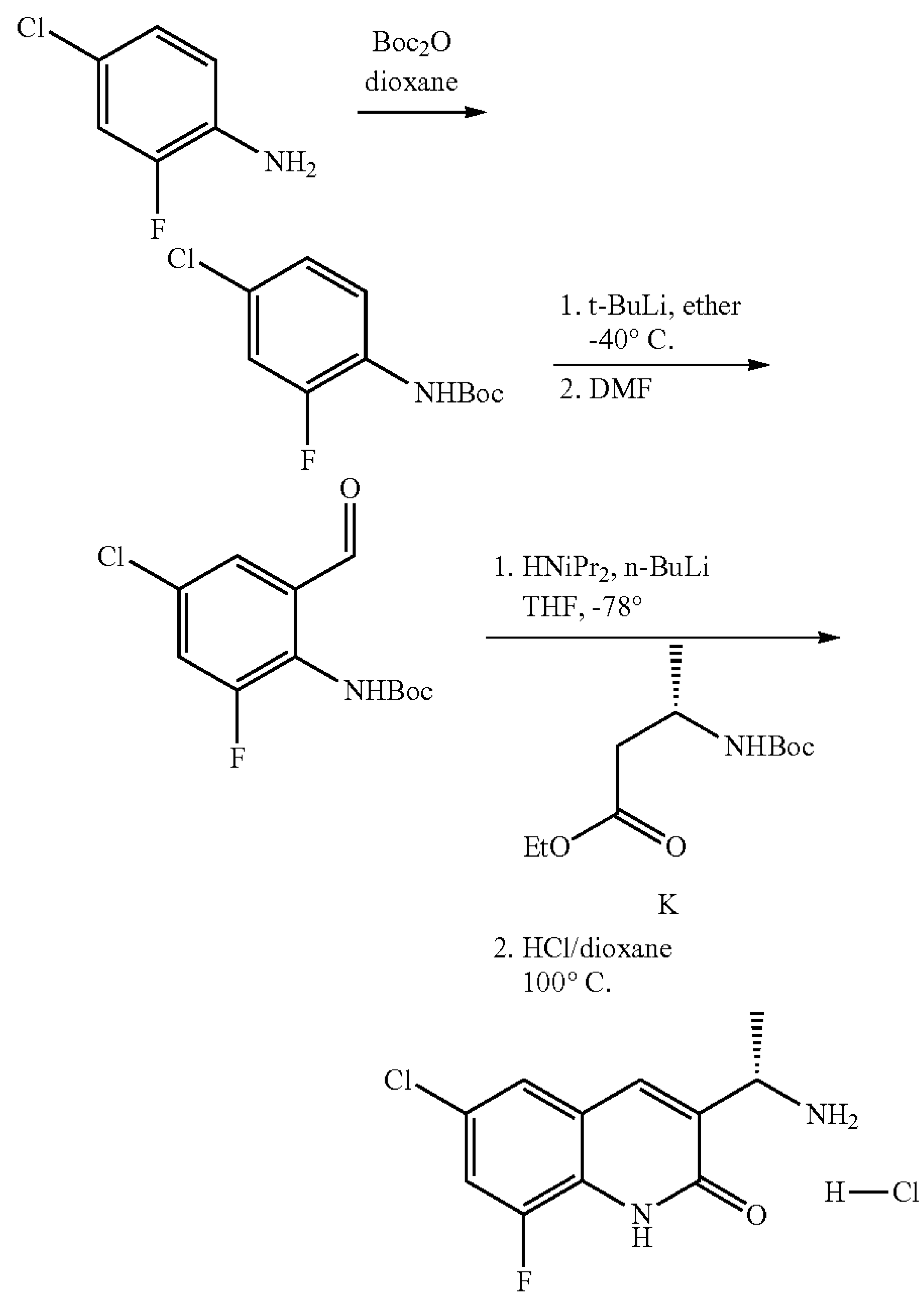
A suspension of (S)-3-aminobutanoic acid (6.25 g, 60.6 mmol) in EtOH (27.5 mL) was cooled on an ice bath. Thionyl chloride (7.5 mL, 103 mmol) was then added dropwise over 40 minutes, during which time the amino acid went into solution. The ice bath was allowed to melt, and the solution was stirred at room temperature overnight. The mixture was evaporated under reduced pressure, and the residue was mixed with more EtOH (60 mL) and again evaporated under reduced pressure to provide an oil. The oil was dissolved in DCM (55 mL) and cooled on an ice bath. TEA (25 mL, 179 mmol) was added dropwise over 15 minutes with stirring, resulting in a milky mixture. Di-tert-butyl dicarbonate (17 mL, 73.2 mmol) was then added. The ice bath was allowed to melt, and the mixture was stirred at room temperature for five days. The resulting mixture was filtered through Celite® 545 on a Buchner funnel, and the filter cake was washed with DCM (50 mL). The filtrate was washed with saturated aqueous citric acid (20 mL) and water (2×100 mL), dried ($MgSO_4$), filtered, and evaporated under reduced pressure to provide the title compound as a clear oil. ^1H NMR is consistent with (5)-ethyl 3-((tert-butoxycarbonyl)amino)butanoate (13.47 g, 58.2 mmol, 96% yield). ^1H NMR (300 MHz, $CDCl_3$): δ ppm 4.95 (br s, 1H), 4.15 (q, J=7.13, 2H), 3.98-4.10 (m, 1H), 2.40-2.57 (m, 2H), 1.44 (s, 9H), 1.27 (t, J=7.18, 3H), 1.22 (d, J=6.74, Hz, 3H).

Step-5 & 6: 3-((S)-1-aminoethyl)-6-chloro-7-((R)-1-(pyridin-2-yl)ethoxy)quinolin-2(1H)-one hydrochloride (II-9)



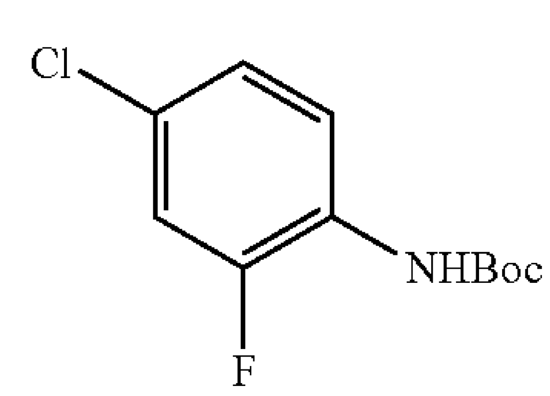
An oven-dried 25 mL round bottom flask and stir bar were placed under an atmosphere of nitrogen. THF (2.25 mL) and diisopropylamine (0.27 mL, 1.894 mmol) were then added by syringe. The solution was cooled using a dry ice/acetone bath (−78° C.) and n-BuLi (1.6 M in hexane, 1.15 mL, 1.84 mmol) was added dropwise over 5 minutes. After stirring for 10 minutes, a solution of (S)-ethyl 3-((tert-butoxycarbonyl)amino)butanoate K (115.3 mg, 0.499 mmol) in THF (0.5 mL) was added dropwise (over 5 minutes). The solution was stirred for 75 minutes at −78° C. and then a solution of (R)-tert-butyl (4-chloro-2-formyl-5-(1-(pyridin-2-yl)ethoxy)phenyl)carbamate (188.7 mg, 0.501 mmol) in THF (1.0 mL) was added dropwise by syringe. The reaction solution became yellow when the aldehyde was added. The reaction was stirred at −78° C. for 13 minutes and then quenched by the addition of saturated aqueous NH_4Cl solution (2.5 mL). The mixture was partitioned between EtOAc and water (10 mL each). The organic layer was dried ($MgSO_4$), filtered, and evaporated under reduced pressure to provide an impure mixture of isomers of (3S)-ethyl 3-((tert-butoxycarbonyl)amino)-2-((2-((tert-butoxycarbonyl)amino)-5-chloro-4-((R)-1-(pyridin-2-yl)ethoxy)phenyl)(hydroxy)methyl)butanoate as a yellow oil (344.8 mg; LCMS: m/z+608 $[M+H]^1$). The crude material (334 mg) was dissolved in 1,4-dioxane (5 mL), treated with 12M aqueous HCl (0.125 mL), and stirred at 110° C. for 90 minutes, during which time a red material precipitated. The mixture was allowed to cool and the supernatant was decanted and discarded. Heptane (~4 mL) was added to the red precipitate remaining in the round bottom and then evaporated under reduced pressure to provide 161.8 mg of a red solid. The material was triturated with ^{i}PrOH (5 mL) and the resulting precipitate was collected on a Hirsch funnel and washed with ^{i}PrOH (1 mL) and ethyl ether (~20 mL) to provide 3-((S)-1-amino ethyl)-6-chloro-7-((R)-1-(pyridin-2-yl)ethoxy)quinolin-2 (1H)-one hydrochloride II-9 (104.2 mg, 0.274 mmol, 55% yield) as a red solid, impure but suitable for use as it is. ^1H NMR (300 MHz, Methanol-d_4): δ ppm 8.81-8.87 (m, 1H), 8.55-8.64 (m, 1H), 8.18 (d, J=7.92 Hz, 1H), 7.96-8.04 (m, 1H), 7.95 (s, 1H), 7.85 (s, 1H), 6.99 (s, 1H), 5.98 (q, J=6.84 Hz, 1H), 4.48 (q, J=6.84 Hz, 1H), 1.86 (d, J=6.45 Hz, 3H), 1.64 (d, J=6.74 Hz, 3H). LCMS (Method 1): m/z 344 $[M+H]^+$.

Example 12—Intermediate II-10: (S)-3-(1-Aminoethyl)-6-chloro-8-fluoroquinolin-2(1H)-one



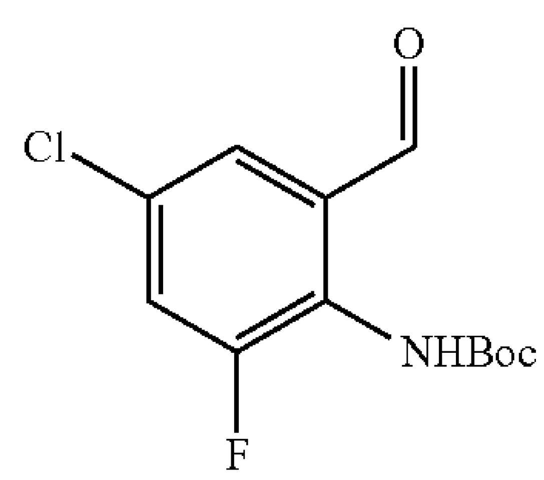
II-10

Step-1: tert-Butyl (4-chloro-2-fluorophenyl)carbamate



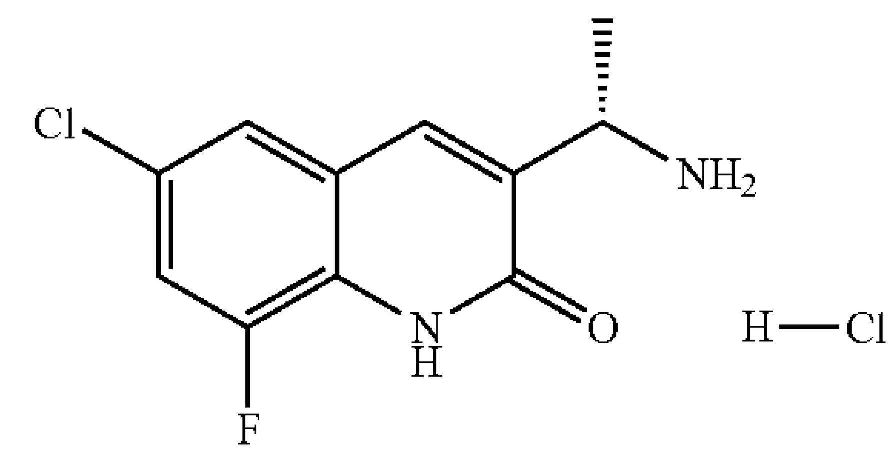
A solution of 4-chloro-2-fluoroaniline (2 g, 13.74 mmol) and di-tert-butyl dicarbonate (6.4 mL, 27.6 mmol) in 1,4-dioxane (50 mL) was stirred at reflux for 2 days. The solvent was then evaporated. The resulting oil was diluted with MeOH, water, and aqueous ammonium hydroxide solution (10 mL each) and vigorously stirred for 45 minutes. The organic lower layer was separated. The organic material was diluted with EtOAc (50 mL), and washed with water (50 mL), 3.6% aqueous HCl solution (2×50 mL), saturated aqueous $NaHCO_3$ solution (50 mL), and then again with water (2×50 mL). The organic layer was dried ($MgSO_4$), filtered, and evaporated under reduced pressure to provide tert-butyl (4-chloro-2-fluorophenyl)carbamate (3.0011 g, 12.22 mmol, 89% yield) as a reddish liquid that solidified on standing. ^1H NMR (300 MHz, DMSO-d_6): δ ppm 9.12 (s, 1H), 7.63 (t, J=8.65 Hz, 1H), 7.42 (dd, J=10.85, 2.35 Hz, 1H), 7.18-7.24 (m, 1H), 1.45 (s, 9H). LCMS (Method 1): m/z 246 $[M+H]^+$.

Step-2: tert-Butyl (4-chloro-2-fluoro-6-formylphenyl)carbamate



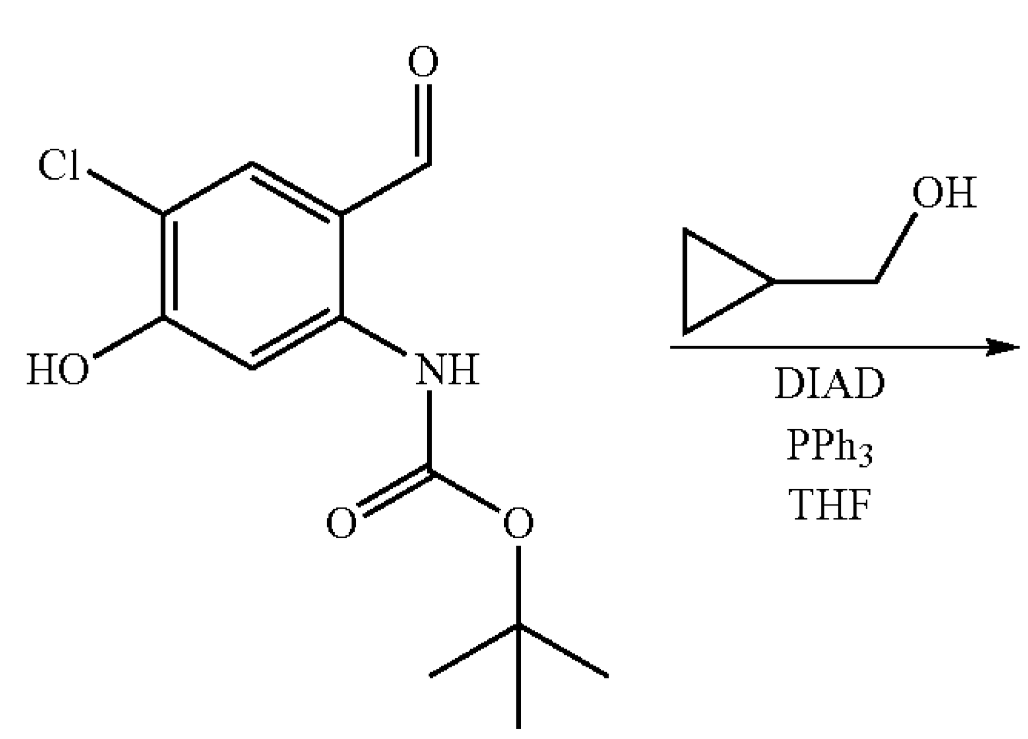
An oven-dried 3-necked 500 mL round bottom flask was fitted with an oven-dried addition funnel and placed under an atmosphere of nitrogen. tert-Butyl (4-chloro-2-fluorophenyl)carbamate (5.44 g, 22.14 mmol) and ethyl ether (91 mL) were added by syringe. The clear solution was cooled on an acetonitrile/dry ice bath (to approximately −40° C.). tert-Butyllithium (1.7M in pentane, 33 mL, 22.14 mmol) was added to the addition funnel by cannula. The t-BuLi solution was added drop wise to the ether solution (over ~10 minutes), during which time the ether solution began to turn orange. The solution was stirred at about −40° C. for 2 hours, during which time it progressively became more orange. DMF (8.7 mL, 112 mmol) was added drop wise (over ~10 minutes), resulting in precipitation of a yellow solid. The MeCN/dry ice bath was replaced with an ice bath and the mixture was stirred for an additional 2 hours. The reaction was then quenched by drop wise addition of water (20 mL), resulting in a brown mixture and the ice bath was removed. The mixture was diluted with EtOAc (100 mL), washed with water (2×100 mL), dried (Na_2SO_4), filtered, and evaporated under reduced pressure to provide 5.45 g of an oily black solid. The material was triturated with hexanes (50 mL), collected on a Buchner funnel and washed with more hexanes to provide 2.73 g tert-butyl (4-chloro-2-fluoro-6-formylphenyl)carbamate as a yellow powder. The filtrate was evaporated under reduced pressure, the residue was triturated in hexanes (~15 mL), and the resulting yellow solid was collected on a Hirsch funnel to provide a second crop of the title compound (0.66 g). A total of 3.39 g (12.4 mmol, 56% yield) of tert-butyl (4-chloro-2-fluoro-6-formylphenyl)carbamate was recovered. ^1H NMR (300 MHz, DMSO-d_6): δ ppm 9.93 (d, J=0.88 Hz, 1H), 9.47 (s, 1H), 7.81-7.90 (m, 1H), 7.55-7.61 (m, 1H), 1.44 (s, 9H). LCMS (Method 1): m/z 296 [M+Na].

Steps-3 & 4: (S)-3-(1-Aminoethyl)-6-chloro-8-fluoroquinolin-2(1H)-one hydrochloride (II-10)



An oven-dried 200 mL round bottom flask and stir bar were placed under an atmosphere of nitrogen. THF (17 mL) and diisopropylamine (1.59 mL, 11.16 mmol) were added by syringe. The resulting solution was cooled on a dry ice/acetone bath (to approximately −78° C.) and then n-butyllithium (1.6M in hexane, 7.1 mL, 11.36 mmol) was added drop wise over a 5 minute period. After stirring for 15 minutes, a solution of (5)-ethyl 3-((tert-butoxycarbonyl)amino)butanoate K (860.7 mg, 3.72 mmol) in THF (3.75 mL) was added drop wise over 5 minutes. The solution was stirred for 80 minutes at −78° C., and a solution of tert-butyl (4-chloro-2-fluoro-6-formylphenyl)carbamate (1016.4 mg, 3.71 mmol) in THF (7.5 mL) was then added drop wise by syringe. The reaction was stirred at −78° C. for another 22 minutes and then quenched by addition of saturated aqueous NH_4Cl solution (17 mL). The mixture was partitioned between EtOAc and water (100 mL each). The organic layer was dried ($MgSO_4$), filtered, and evaporated under reduced pressure to provide 1.88 g of the title compound as an orange gum. The material was dissolved in 1,4-dioxane (38 mL), treated with 12M aqueous HCl (0.96 mL), and stirred at 110° C. for 50 minutes. The sample was then allowed to cool. The solvent was evaporated under reduced pressure to provide 1.24 g of a red solid. The material was triturated in IPA (25 mL), collected on a Hirsch funnel and washed sequentially with IPA (5 mL) and ethyl ether (~20 mL) to provide (S)-3-(1-aminoethyl)-6-chloro-8-fluoroquinolin-2(1H)-one hydrochloride (370.4 mg, 1.337 mmol, 36% yield) as a red solid. ^1H NMR (300 MHz, DMSO-d_6): δ ppm 12.41 (s, 1H), 8.33 (br s, 3H), 8.10 (s, 1H), 7.67-7.76 (m, 2H), 4.38-4.53 (m, 1H), 1.52 (d, J=7.04 Hz, 3H). LCMS (Method 1): m/z 241 $[M+H]^+$.

Example 13—Intermediate II-11: (S)-3-(1-aminoethyl)-6-chloro-7-(cyclopropylmethoxy) quinolin-2 (1H)one



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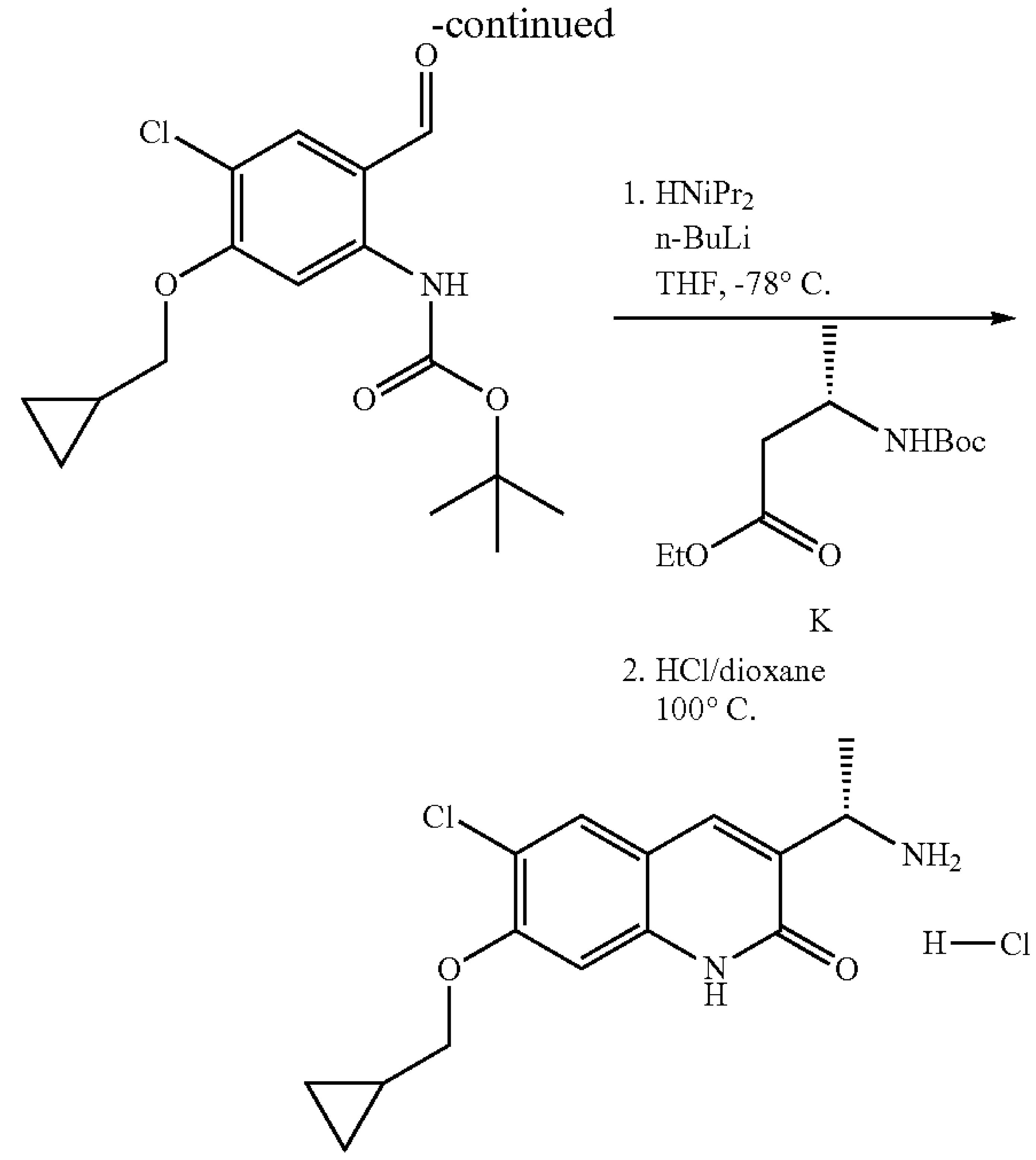
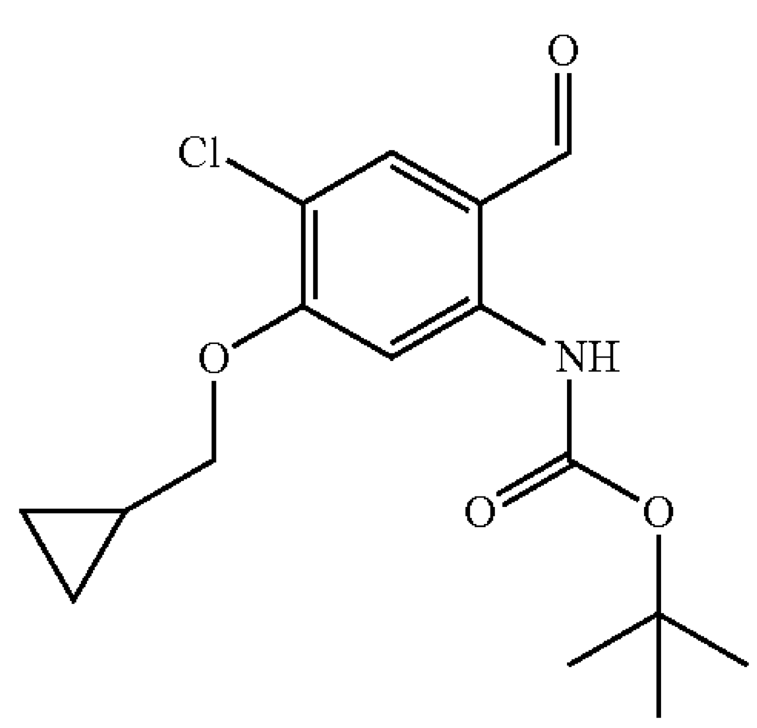


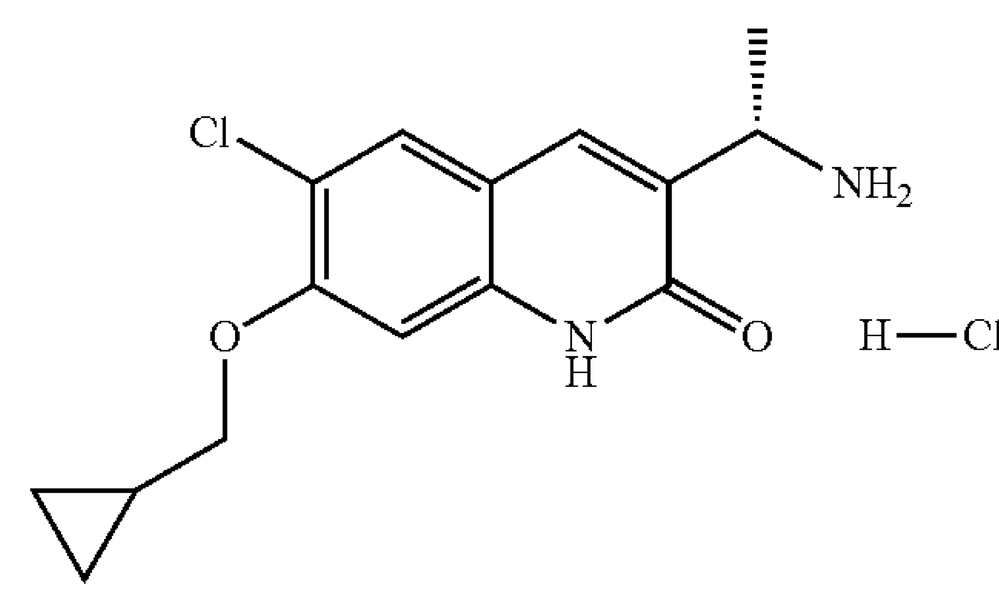
II-11

Step-1: tert-butyl (4-chloro-5-(cyclopropylmethoxy)-2-formylphenyl)carbamate



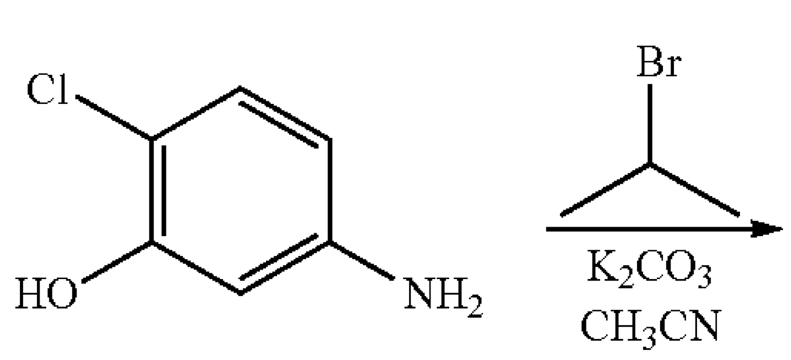
A mixture of cyclopropylmethanol (0.145 mL, 1.838 mmol), tert-butyl (4-chloro-2-formyl-5-hydroxyphenyl)carbamate J (499.4 mg, 1.838 mmol) and triphenylphosphine (579.4 mg, 2.209 mmol) was placed in a 100 mL round bottom flask under an atmosphere of nitrogen and THF (20 mL) was then added by syringe. The resulting orange solution was cooled on an ice bath and DIAD (0.43 mL, 2.184 mmol) was added dropwise. The ice bath was removed and the solution was stirred at room temperature for 48 hours. Once LCMS indicated the reaction had gone to completion, silica gel was added and the solvent was evaporated under reduced pressure. The sample was purified by column chromatography on a Biotage® MPLC chromatography system using a 25 g silica gel column eluted with 0 to 3% EtOAc in hexanes to provide tert-butyl (4-chloro-5-(cyclopropylmethoxy)-2-formylphenyl)carbamate (410.6 mg, 1.260 mmol, 68.6% yield) as a yellowish solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ ppm 10.57 (s, 1H), 9.75 (s, 1H), 7.95-8.00 (m, 2H), 4.02 (d, J=7.04 Hz, 2H), 1.49 (s, 9H), 1.23-1.31 (m, 1H), 0.57-0.66 (m, 2H), 0.38-0.46 (m, 2H). LCMS (Method 1): m/z 270 (loss of t-Bu).

Step-2 & 3: (S)-3-(1-aminoethyl)-6-chloro-7-(cyclopropylmethoxy)quinolin-2(1H)-one hydrochloride (II-11)



An oven-dried 25 mL round bottom flask and stir bar were placed under an atmosphere of nitrogen and THF (5.6 mL) and diisopropylamine (0.53 mL, 3.72 mmol) were added by syringe. The solution was cooled on a dry ice/acetone bath (to −78° C.) and n-BuLi (1.6 M in hexane, 2.35 mL, 3.76 mmol) was added dropwise over a 5 minute period. After stirring for 15 minutes, a solution of (5)-ethyl 3-((tert-butoxycarbonyl)amino)butanoate K (286 mg, 1.238 mmol) in THF (1.25 mL) was added dropwise (over 5 minutes). The solution was stirred for 80 minutes at −78° C. and a solution of tert-butyl (4-chloro-5-(cyclopropylmethoxy)-2-formylphenyl)carbamate (403.2 mg, 1.238 mmol) in THF (2.5 mL) was added dropwise by syringe. The reaction solution became yellow when the aldehyde was added. The reaction was stirred at −78° C. for 12 minutes and then quenched by addition of saturated aqueous NH_4Cl solution (6 mL). The mixture was partitioned between EtOAc and water (25 mL each) and the organic layer was dried ($MgSO_4$), filtered, and evaporated under reduced pressure to provide 724.5 g of a yellowish oil. The material was dissolved in 1,4-dioxane (12.5 mL), treated with 12M HCl (aqueous; 0.32 mL), and stirred at 110° C. for 70 minutes during which time the solution became thick with a pink precipitate. The sample was allowed to cool and the solvent was evaporated under reduced pressure to provide 1.13 g of a fibrous red solid. The material was triturated with i-PrOH (15 mL) and the resulting precipitate was collected on a Buchner funnel and washed with i-PrOH (20 mL) and ethyl ether (~60 mL) to provide (S)-3-(1-aminoethyl)-6-chloro-7-(cyclopropylmethoxy)quinolin-2(1H)-one hydrochloride (146.1 mg, 0.444 mmol, 36% yield) as a papery white solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ ppm 12.13 (br s, 1H), 8.21 (br s, 3H), 7.98 (s, 1H), 7.86 (s, 1H), 6.98 (s, 1H), 4.32-4.46 (m, 1H), 3.96 (d, J=6.40 Hz, 2H), 1.51 (d, J=6.70 Hz, 3H), 1.21-1.35 (m, 1H), 0.55-0.68 (m, 2H), 0.35-0.46 (m, 2H). LCMS (Method 1): m/z 293 $[M+H]^+$.

Example 14—Intermediate II-12: S)-3-(1-Aminoethyl)-6-chloro-7-isopropoxyquinolin-2(1H)-one hydrochloride salt



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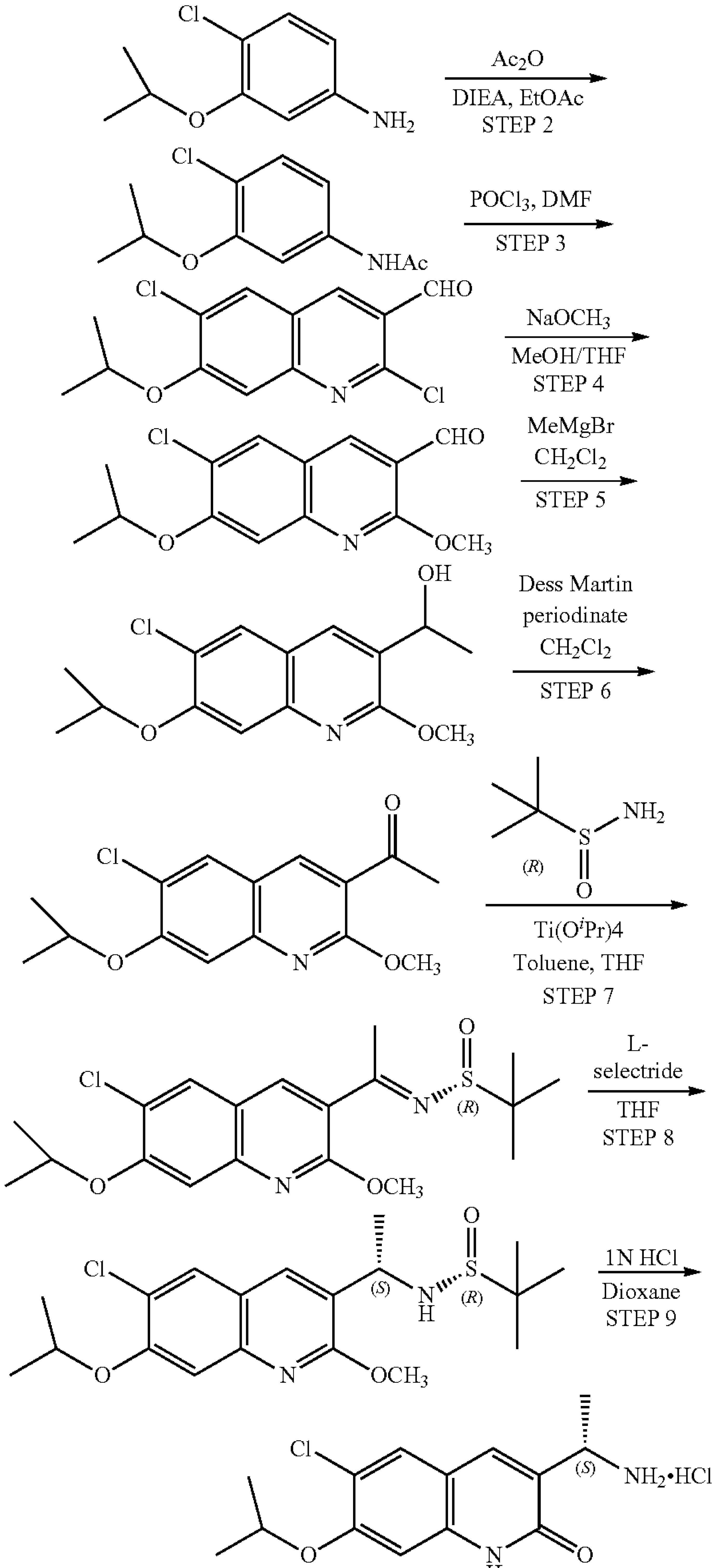
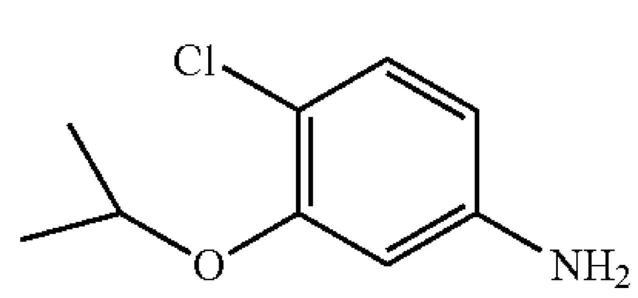


II-12

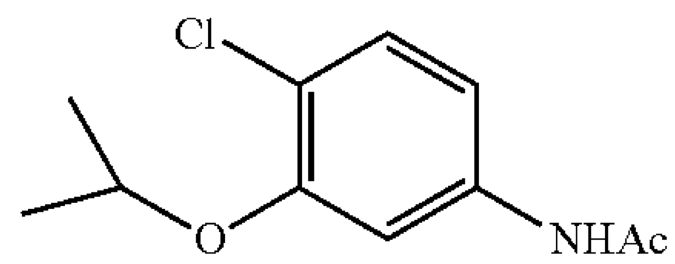
Step-1: 4-Chloro-3-isopropoxyaniline



A mixture of 5-amino-2-chlorophenol (20 g, 139 mmol) and 2-bromopropane (26 mL, 278 mmol) and K_2CO_3 (38.4 g, 278 mmol) in CH_3CN (300 mL) was refluxed for 24 h. The reaction mixture was cooled to room temperature, filtered and the solid was washed with ethyl acetate (150

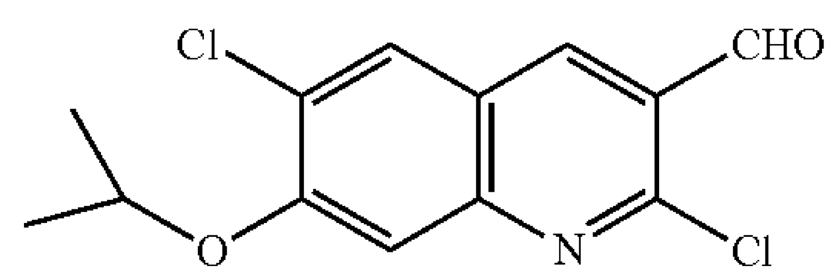
mL). The filtrate was concentrated and the residue was purified by ISCO (SiO_2: Hex/EtOAc 0 to 40%) to give the title compound (22.6 g, 87%).

Step-1: N-(4-Chloro-3-isopropoxyphenyl)acetamide



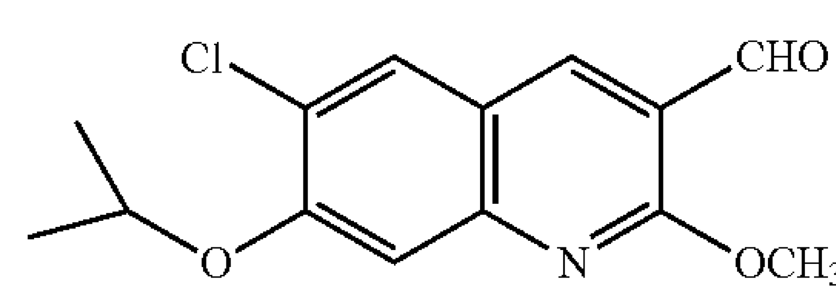
To a mixture of 4-chloro-3-isopropoxyaniline (22.5 g, 121 mmol) in CH_2Cl_2 (200 mL) was added DIEA (42 mL, 242 mmol) followed by acetic anhydride (17 mL, 181 mmol). The resultant mixture was stirred at room temperature for 3 h. Upon the completion of the reaction, water (100 mL) was added and stirred for 10 minutes. The organic layer was separated, washed with 1N HCl (aq, 200 mL), brine (150 mL) and dried over anhydrous Na_2SO_4. The solution was filtered and concentrated. The crude residue was recrystallized from CH_2Cl_2/hexanes to give desired compound (19.6 g, 71%).

Step-3: 2,6-Dichloro-7-isopropoxyquinoline-3-carbaldehyde



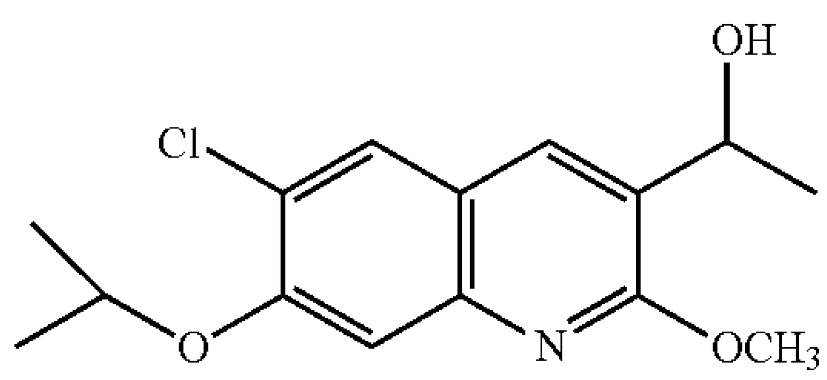
DMF (15 mL, 193.6 mmol) was added to a 350 mL seal tube and cooled to 0° C. To this solution was added phosphorous oxychloride (60 mL, 645.6 mmol) drop wise during 40-50 min. The resultant mixture was brought to room temperature followed by addition of N-(4-chloro-3-isopropoxyphenyl)acetamide (14.7 g, 64.5 mmol) in portions and heated at 80° C. overnight. The mixture was cooled to room temperature and carefully poured onto crushed ice. The yellow precipitate was filtered, washed with water and dried over P_2O_5 overnight to afford the title compound as yellow solid (17.5 g, 95%).

Step-4: 6-Chloro-7-isopropoxy-2-methoxyquinoline-3-carbaldehyde



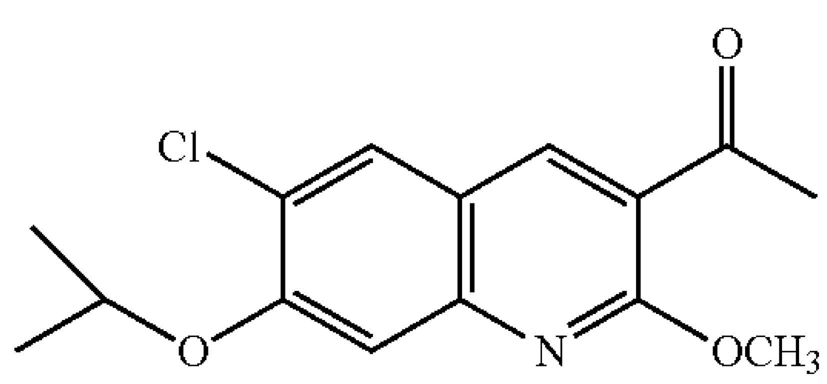
To 2,6-dichloro-7-isopropoxyquinoline-3-carbaldehyde (5.8 g, 20.4 mmol) in a co-solvent of MeOH:THF (1:1, 100 mL) was added NaOMe (2.2 g, 40.8 mmol) portion wise at room temperature. The reaction mixture was refluxed for 3 h. After cooling to room temperature, the reaction was quenched with aqueous NH_4.Cl solution (20 mL). The mixture was extracted with EtOAc (25 mL×3). The combined organic layer was dried (Na_2SO_4), concentrated and purified by flash chromatography with Hexane/EtOAc (3:1) to give the desired product (5.07 g, 89%) as a yellow solid.

Step-5: 1-(6-Chloro-7-isopropoxy-2-methoxyquinolin-3-yl)methanol



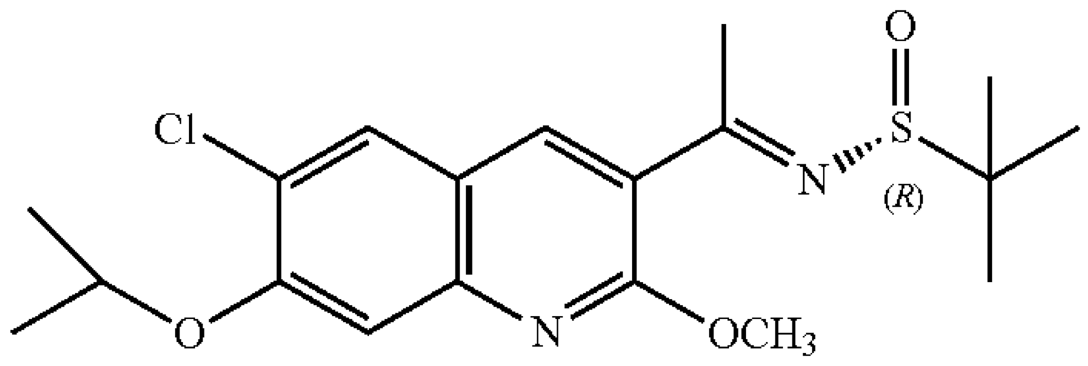
To 6-chloro-7-isopropoxy-2-methoxyquinoline-3-carbaldehyde (5.07 g, 18.17 mmol) in THF (100 mL) at −78° C. was added a solution of MeMgCl in THF (3 M, 9.1 mL, 27.2 mmol) drop wise. The reaction was stirred at rt for 3 h and then quenched with aqueous NH_4Cl solution (50 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (25 mL×3). The combined organic layers were dried (Na_2SO_4), concentrated, and purified by silica gel chromatography with hexane/EtOAc (3:1) to give the title compound (4.06 g, 76%).

Step-6: 1-(6-Chloro-7-isopropoxy-2-methoxyquinolin-3-yl)ethanone



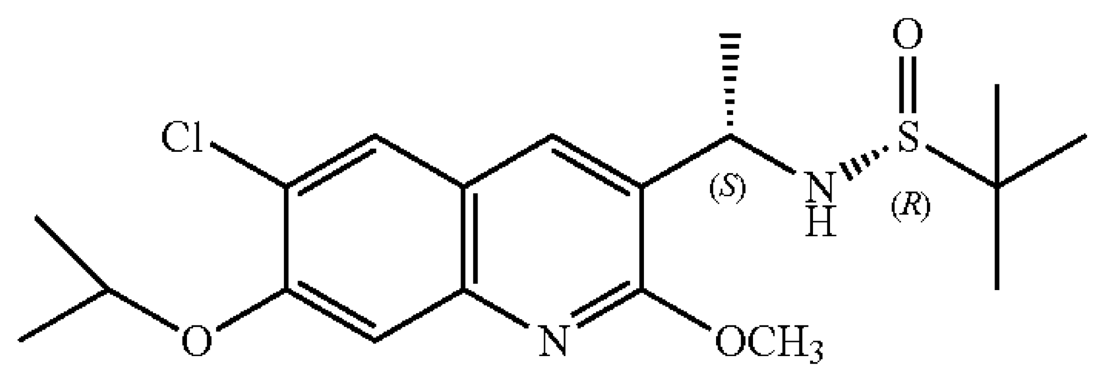
To 1-(6-chloro-7-isopropoxy-2-methoxyquinolin-3-yl) ethanol (4.06 g, 13.8 mmol) in CH_2Cl_2 (50 mL) at rt was added DMP (7.0 g, 16.5 mmol) portion wise. The reaction was stirred at room temperature for 2. h, and then was quenched with an aqueous solution of $NaHCO_3$ and $Na_2S_2O_3$. After stirring for 15 min, both layers became clear. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (30 mL×2). The combined organic layers were dried (Na_2SO_4), concentrated and purified by silica gel chromatography with hexane/EtOAc (4:1) to give the title compound (3.67 g, 72%) as a white solid.

Step-7: (R,E)-N-(1-(6-chloro-7-isopropoxy-2-methoxyquinolin-3-yl)ethylidene)-2-methyl propane-2-sulfinamide



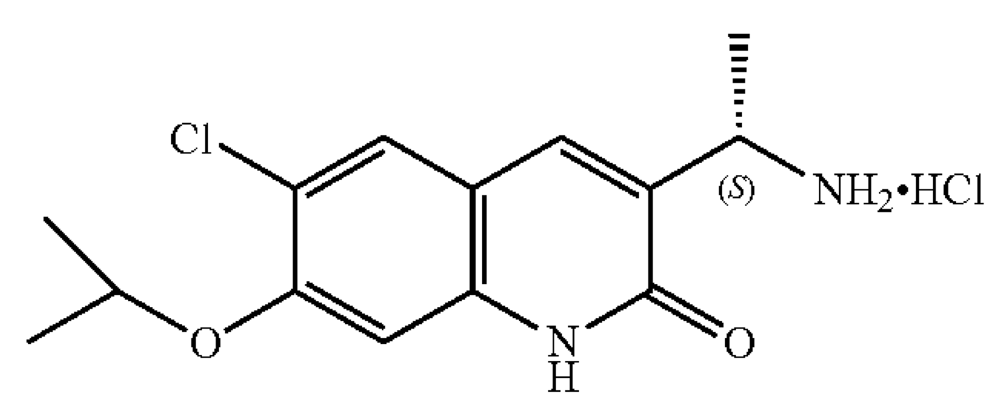
To 1-(6-chloro-7-isopropoxy-2-methoxyquinolin-3-yl) ethanone (3.67 g, 12.5 mmol) in THF/toluene (20 mL:400 mL) at room temperature was added (R)-2-methylpropane-2-sulfinamide (3.03 g, 25 mmol) and $Ti(O^iPr)_4$ (11 mL, 37.5 mmol,). The reaction was refluxed with a Dean-Stark apparatus. After the reaction was refluxed for 4 h and 150 mL of solvent was removed, the reaction was cooled to rt. The solvent was removed under vacuum, and 50 mL of EtOAc was added to the residue, followed by addition of 20 mL of saturated aqueous $NaHCO_3$ solution. After stirring for 10 min, the solid was removed through a pad of celite. The filtrate was extracted with EtOAc (200 mL×2), dried (Na_2SO_4), concentrated and purified by silica gel chromatography with hexane/EtOAc (1:1) to give compound (4.32 g, 87%).

Step-8: (R)—N—((S)-1-(6-chloro-7-isopropoxy-2-methoxyquinolin-3-yl)ethyl)-2-methyl propane-2-sulfinamide



To (R,E)-N-(1-(6-chloro-7-isopropoxy-L-methoxyquinolin-3-yl)ethylidene)-2-methyl propane-2-sulfinamide (4.32 g, 10.9 mmol) in THF (100 mL) at −78° C., was added 1 M L-selectride (14.2 mL, 14.2 mmol) in THF drop wise. The reaction mixture was warmed to rt and stirred for 3 h. The reaction was quenched with aqueous saturated NH_4Cl (30 mL) solution and then extracted with EtOAc (20 mL×3). The combined organic layers were dried (Na_2SO_4), concentrated and purified by silica gel chromatography with hexane/EtOAc (1:1) to give the title compound (3.58 g, 82%).

Step-9: (S)-3-(1-aminoethyl)-6-chloro-7-isopropoxyquinolin-2(1H)-one hydrochloride salt (II-12)



To (R)—N—((S)-1-(6-chloro-1-isopropoxy-2-methoxyquinolin-3-yl)ethyl)-2-methyl propane-2-sulfinamide (3.58 g, 8.99 mmol) in dioxane (50 mL) was added 2 N HCl (50 mL) at rt. The reaction was refluxed for 3 h. The solvent was removed under vacuum and the residue was dried under vacuum to afford crude product, which was further purified by trituration (CH_2Cl_2/MeOH/hexane) to give pure compound II-12 (2.44 g, 86%) as a white solid. ^1H NMR (300 MHz, DMSO-d6): δ 12.10 (s, 1H), 8.29 (br, s, 3H), 7.98 (s, 1H), 7.83 (s, 1H), 7.08 (s, 1H), 4.66 (m, 1H), 4.38 (m, 1H), 3.91 (s, 3H), 1.52 (d, J=6.87 Hz, 3H), 1.37 (d, J=6.03 Hz, 6H). LCMS (Method 3): Rt 8.06 min, m/z 281.1 $[M+H]^+$.

TABLE 1

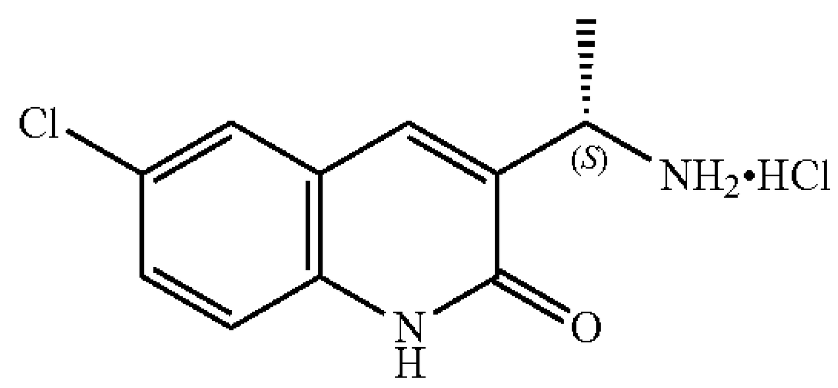
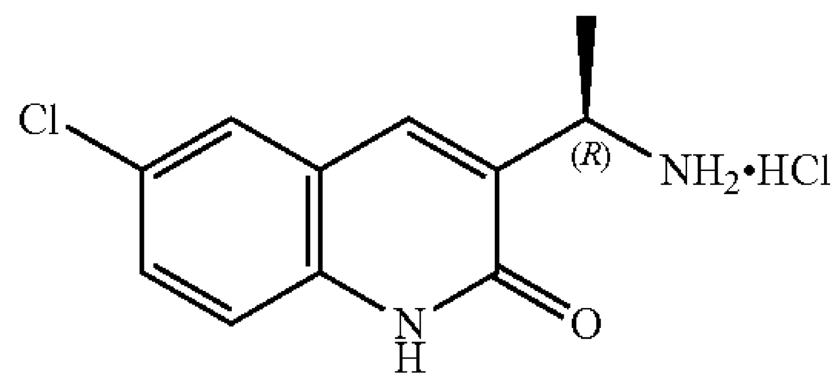
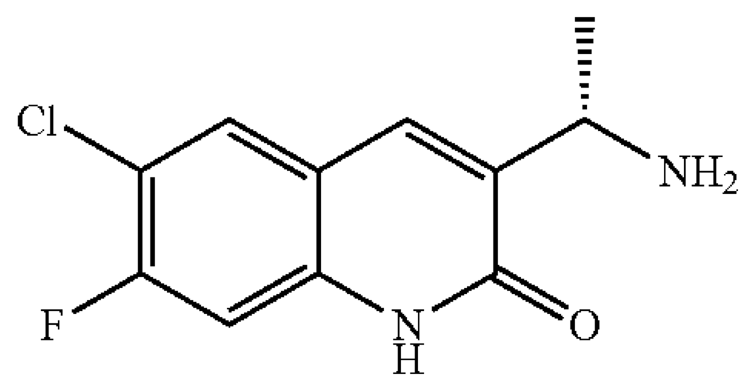
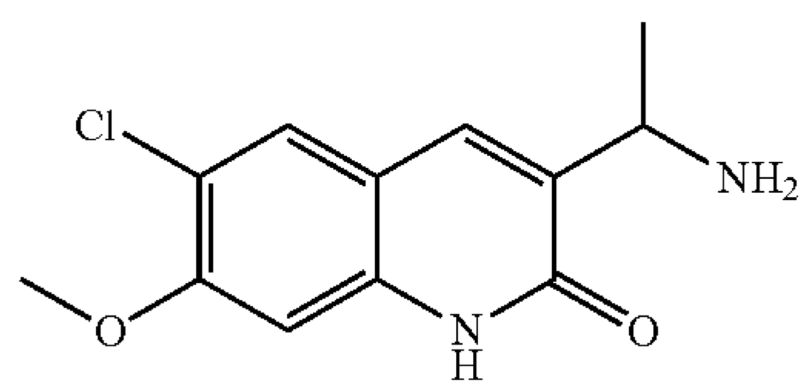
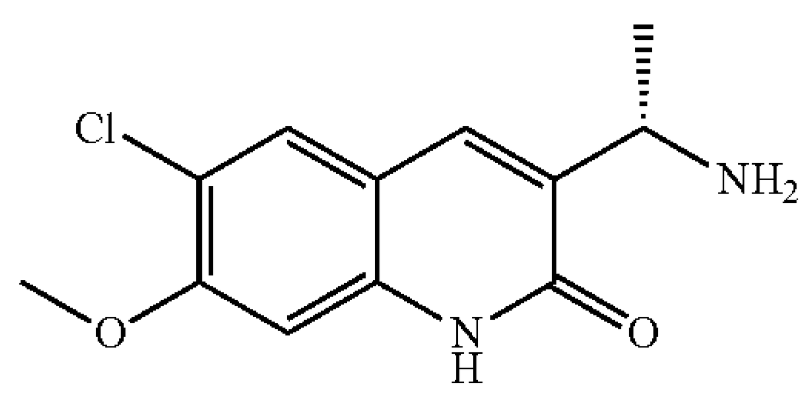
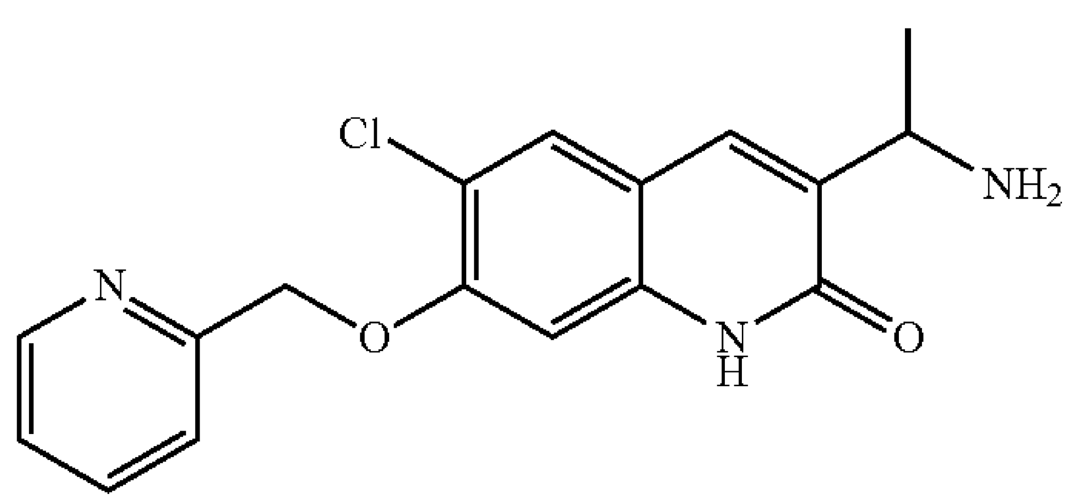
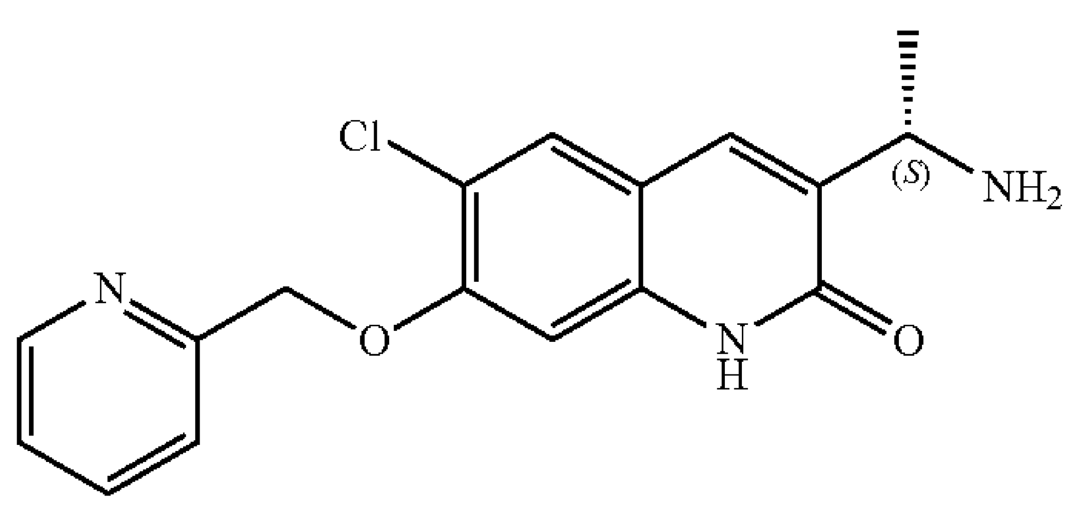
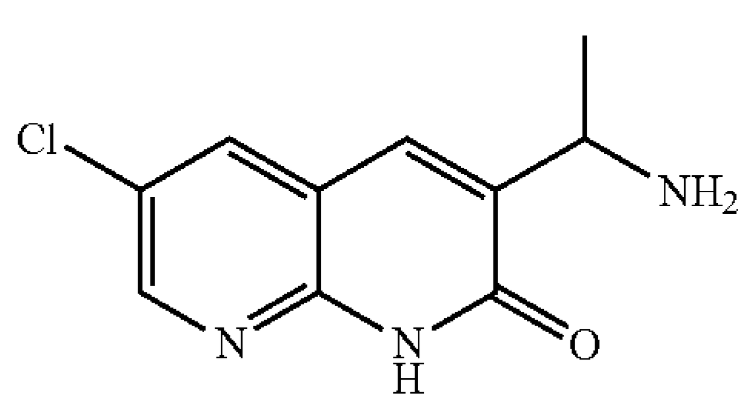
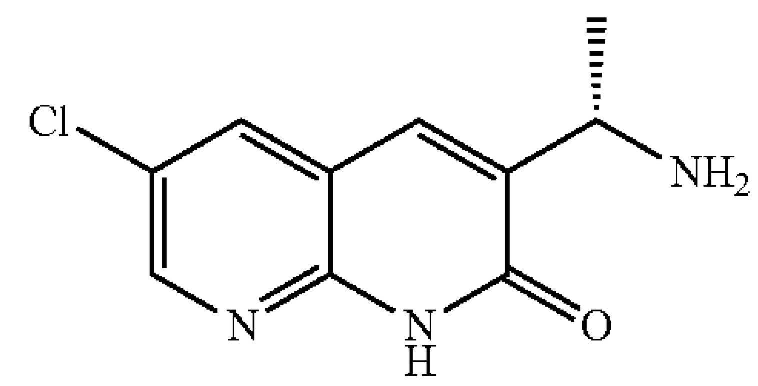
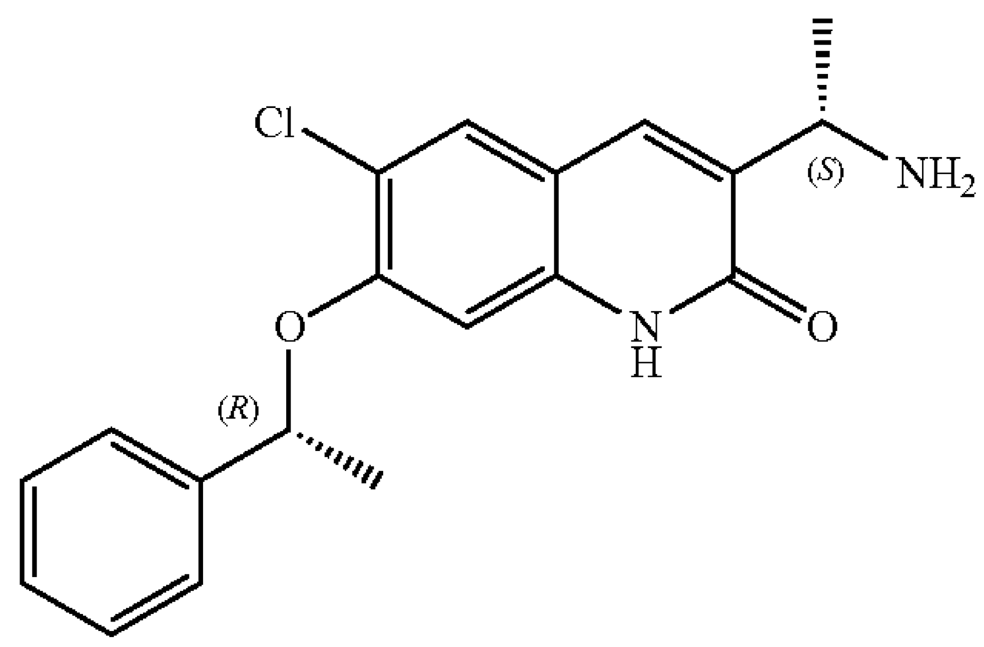
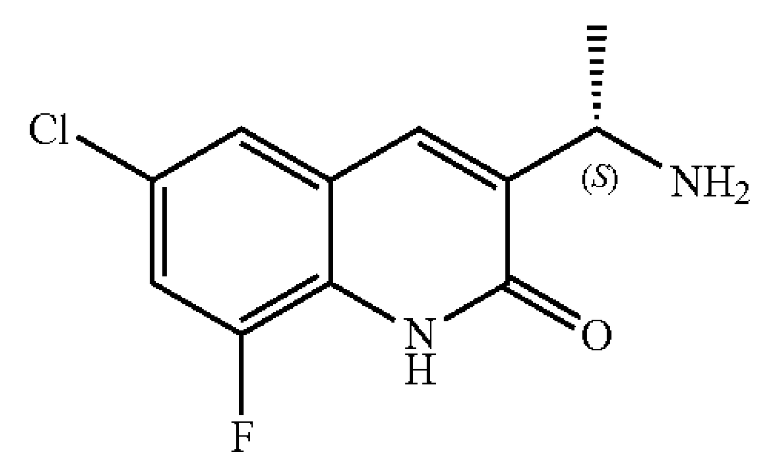
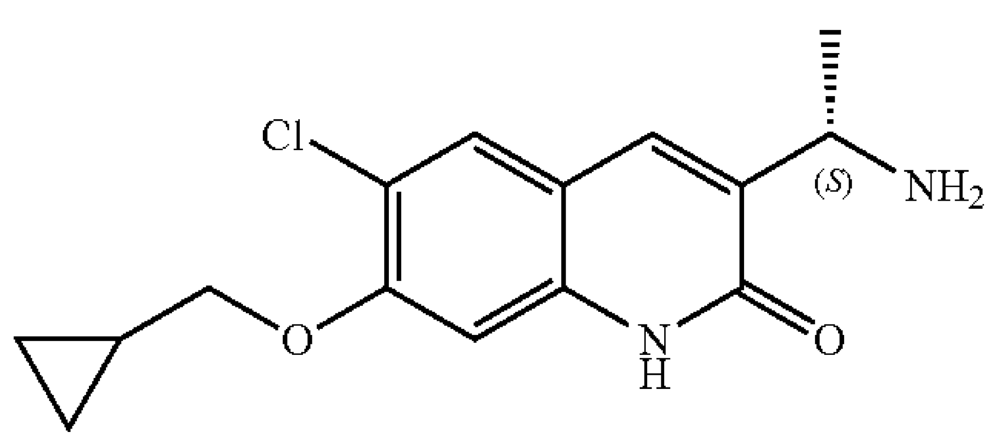
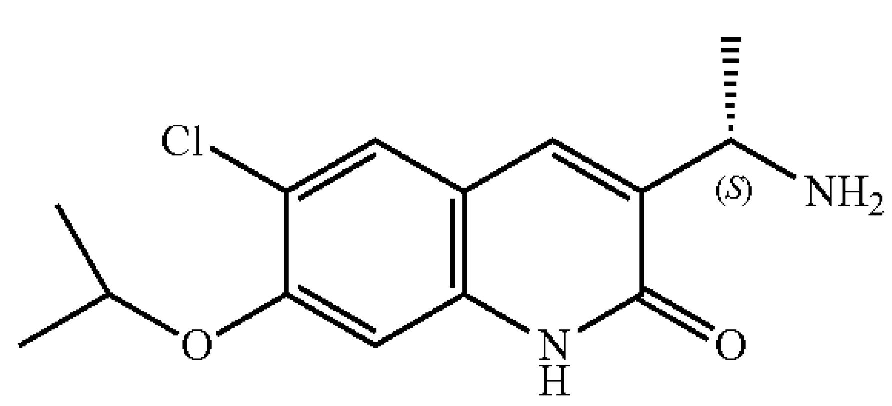
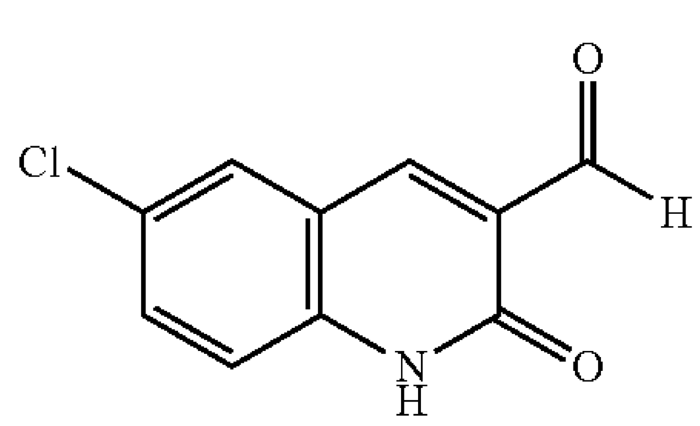
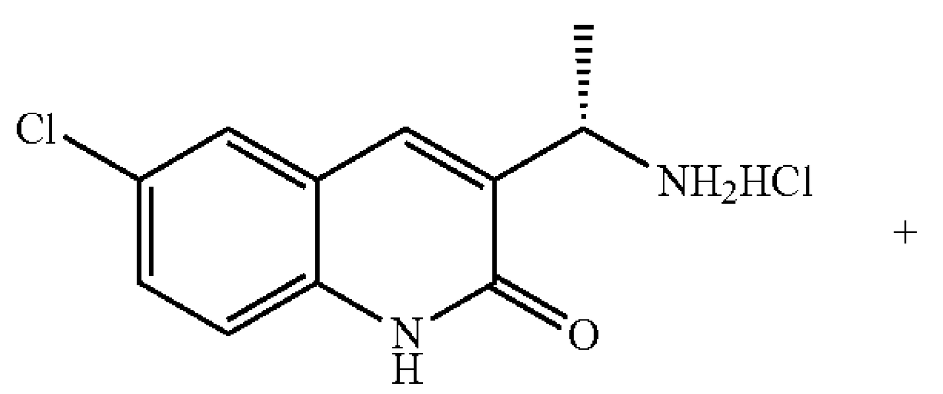
Intermediate No.	Chemical names	Structure
	The Intermediates listed in Table 1 were either prepared using the methods described above or obtained from commercial sources.	
II-1	(S)-3-(1-aminoethyl)-6-chloroquinolin-2(1H)-one hydrochloride	
II-2	(R)-3-(1-aminoethyl)-6-chloroquinolin-2(1H)-one hydrochloride	
II-3	(S)-3-(1-aminoethyl)-6-chloro-7-fluoroquinolin-2(1H)-one	
II-4	3-(1-aminoethyl)-6-chloro-7-methoxyquinolin-2(1H)-one	
II-5	(S)-3-(1-aminoethyl)-6-chloro-7-methoxyquinolin-2(1H)-one	
II-6	3-(1-aminoethyl)-6-chloro-7-(pyridin-2-ylmethoxy)quinolin-2(1H)-one	
II-7	(S)-3-(1-aminoethyl)-6-chloro-7-(pyridin-2-ylmethoxy)quinolin-2(1H)-one	
II-8	3-(1-aminoethyl)-6-chloro-1,8-naphthyridin-2(1H)-one	

TABLE 1-continued

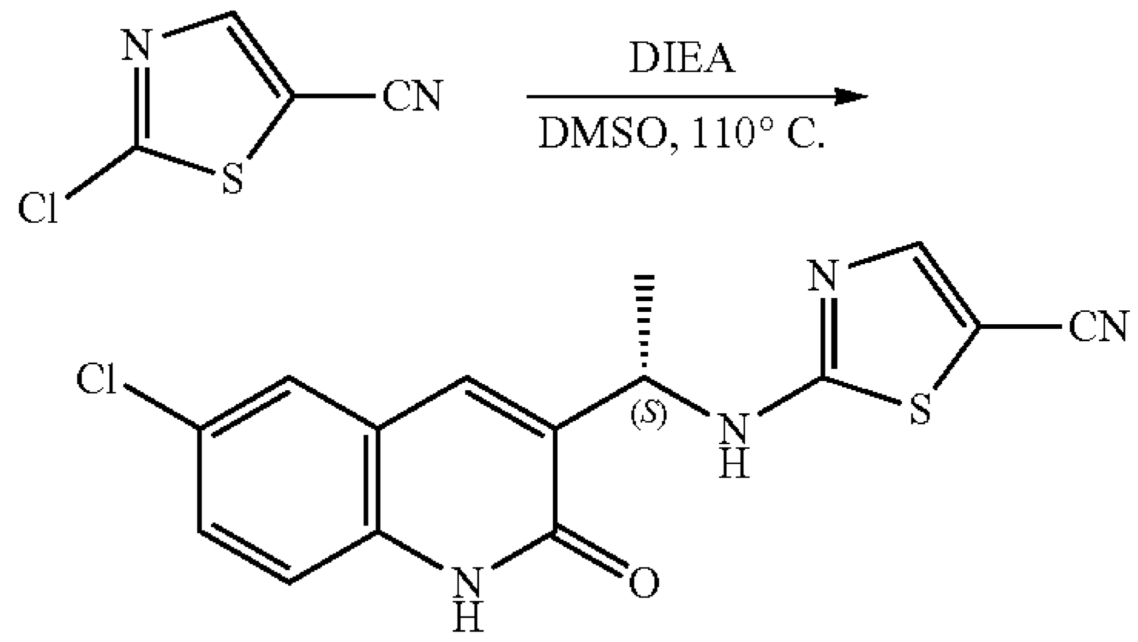
The Intermediates listed in Table 1 were either prepared using the methods described above or obtained from commercial sources.

Intermediate No.	Chemical names	Structure
II-8a	(S)-3-(1-aminoethyl)-6-chloro-1,8-naphthyridin-2(1H)-one	
II-9	(3-((S)-1-aminoethyl)-6-chloro-7-((R)-1-(pyridin-2-yl)ethoxy)quinolin-2(1H)-one	
II-10	(S)-3-(1-aminoethyl)-6-chloro-8-fluoroquinolin-2(1H)-one	
II-11	(S)-3-(1-aminoethyl)-6-chloro-7-(cyclopropylmethoxy) quinolin-2(1H)-one	
II-12	(S)-3-(1-aminoethyl)-6-chloro-7-isopropoxy quinolin-2(1H)-one	
IV	6-chloro-2-oxo-1,2-dihydroquinoline-3-carbaldehyde	

Example 15—(S)-2-((1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)amino)thiazole-5-carbonitrile (I-1)



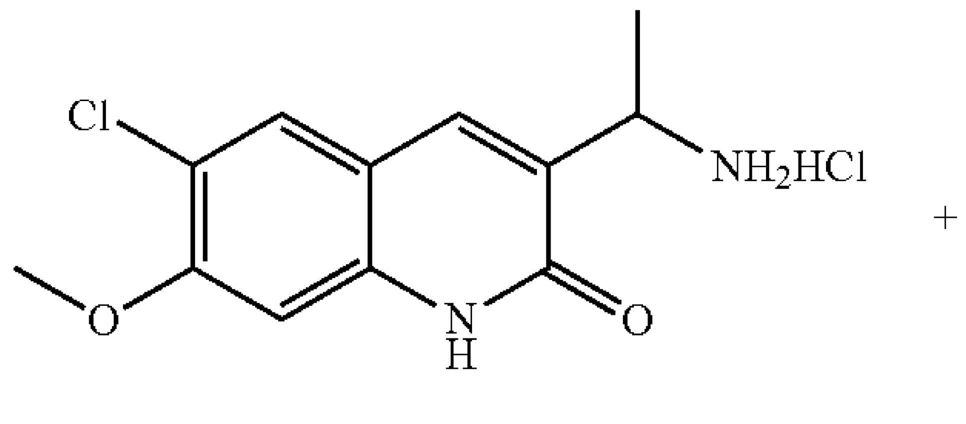
II-1



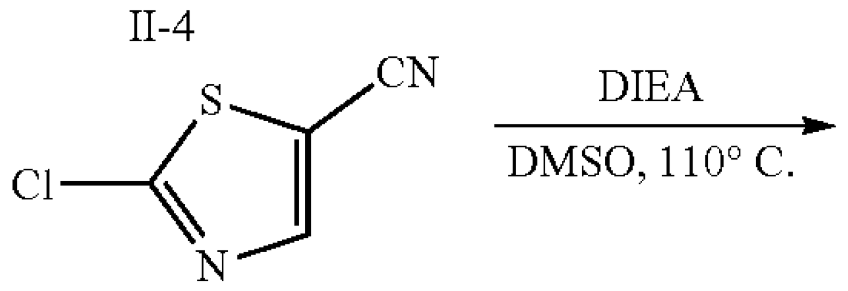
I-1

A mixture of 2-chlorothiazole-5-carbonitrile (250 mg, 1.73 mmol), (S)-3-(1-aminoethyl)-6-chloroquinolin-2(1H)-one hydrochloride II-1 (582 mg, 2.25 mmol) and N,N-diisopropyl ethylamine (0.84 mL, 4.84 mmol) in anhydrous dimethyl sulfoxide (9 mL) was heated to 110° C. and stirred overnight under N_2. After cooling to room temperature, the mixture was partitioned between EtOAc/10% citric acid (aq.) and filtered. The organic layer was separated, washed with water (3×), brine, dried (Na_2SO_4) and concentrated in vacuum. The residue was purified on ISCO (40 g silica gel column, MeOH/dichloromethane 0-10%; C18 reversed-phase column, 130 g, MeOH/H_2O). The off-white solid obtained was triturated with ether and filtered. It was then dissolved in MeOH and concentrated in vacuum for four times. The residue was mixed with water and lyophilized to afford the desired product I-1 as a cream solid (341 mg, 60%). m.p. 211-213° C. (dec.). ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm: 12.04 (s, 1H), 9.19 (d, J=6.9 Hz, 1H), 7.87 (s, 1H), 7.81 (d, J=2.5 Hz, 1H), 7.77 (s, 1H), 7.51 (dd, J=8.8, 2.2 Hz, 1H), 7.31 (d, J=8.5 Hz, 1H), 4.97 (m, 1H), 1.46 (d, J=6.9 Hz, 3H). LCMS (LCMS 3): 99% pure @ 254 nm, Rt 4.93 min, m/z 331, 333 $[M+H]^+$.

Example 16—2-((1-(6-chloro-7-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)amino) thiazole-5-carbonitrile (I-2)



II-4



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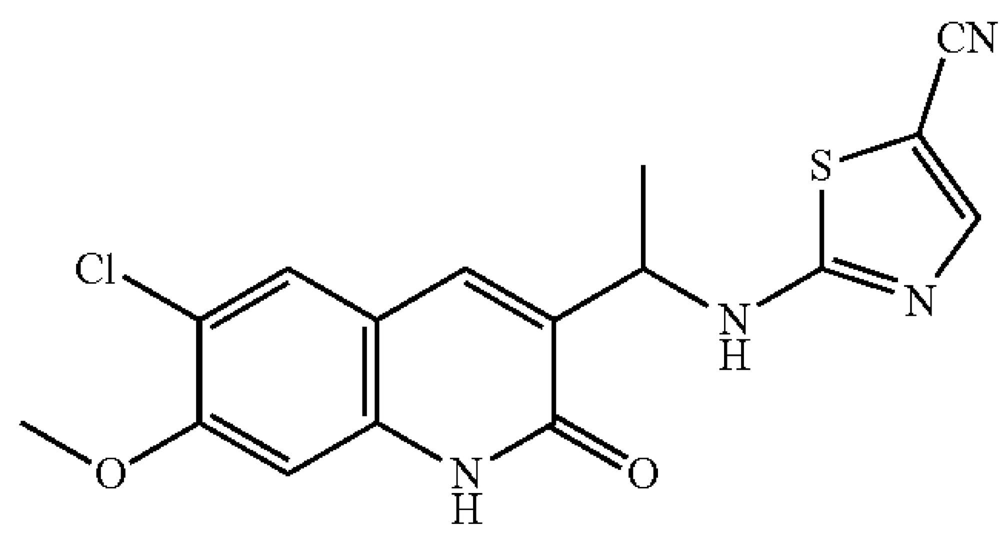
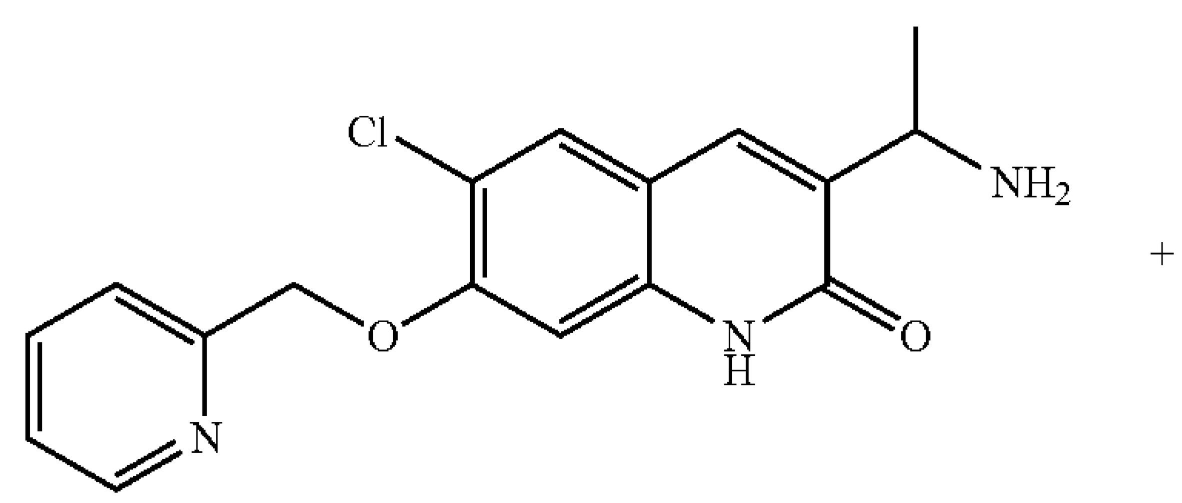


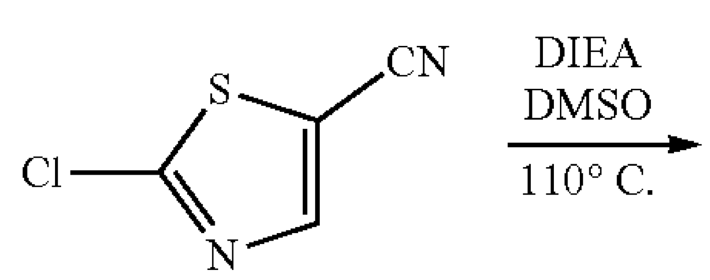
I-2

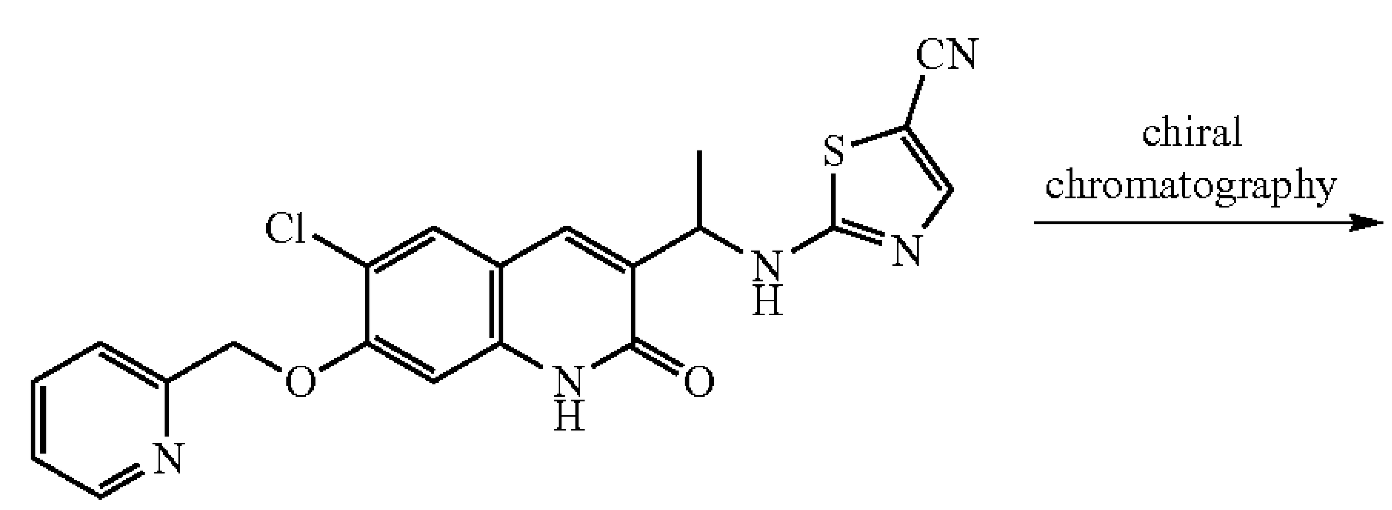
A mixture of 2-chlorothiazole-5-carbonitrile (38.8 mg, 0.268 mmol) and 3-(1-aminoethyl)-6-chloro-7-methoxyquinolin-2(1H)-one hydrochloride II-4 (69.7 mg, 0.241 mmol) was treated with DMSO (1.5 ml) and DIEA (126 μL, 0.721 mmol). The solution was stirred at 110° C. for eight hours. The sample was mixed with water (20 mL) and extracted with EtOAc (2×15 mL). The extracts were dried (Na_2SO_4) and filtered, silica gel was added, and the solvent was evaporated under reduced pressure. The material was chromatographed by Biotage MPLC (10 g silica gel column) with 0 to 100% EtOAc in hexanes, with isocratic elution when peaks came off to provide 2-((1-(6-chloro-7-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)amino) thiazole-5-carbonitrile (57.7 mg, 0.160 mmol, 66.3% yield, HPLC purity 100% at 220 nm) as a brownish solid. 1H NMR (300 MHz, DMSO-d6): δ ppm 11.90 (s, 1H), 9.16 (br d, J=7.04 Hz, 1H), 7.85-7.88 (m, 1H), 7.82 (s, 1H), 7.70 (s, 1H), 6.95 (s, 1H), 4.87-5.00 (m, 1H), 3.88 (s, 3H), 1.44 (d, J=6.74 Hz, 3H). LCMS (Method 1): Rt 2.33 min., m/z 360.86 [M+J]+.

Example 17—2-((1-(6-chloro-2-oxo-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-3-yl)ethyl)amino) thiazole-5-carbonitrile (I-3, I-4, and I-5)



II-6





I-3

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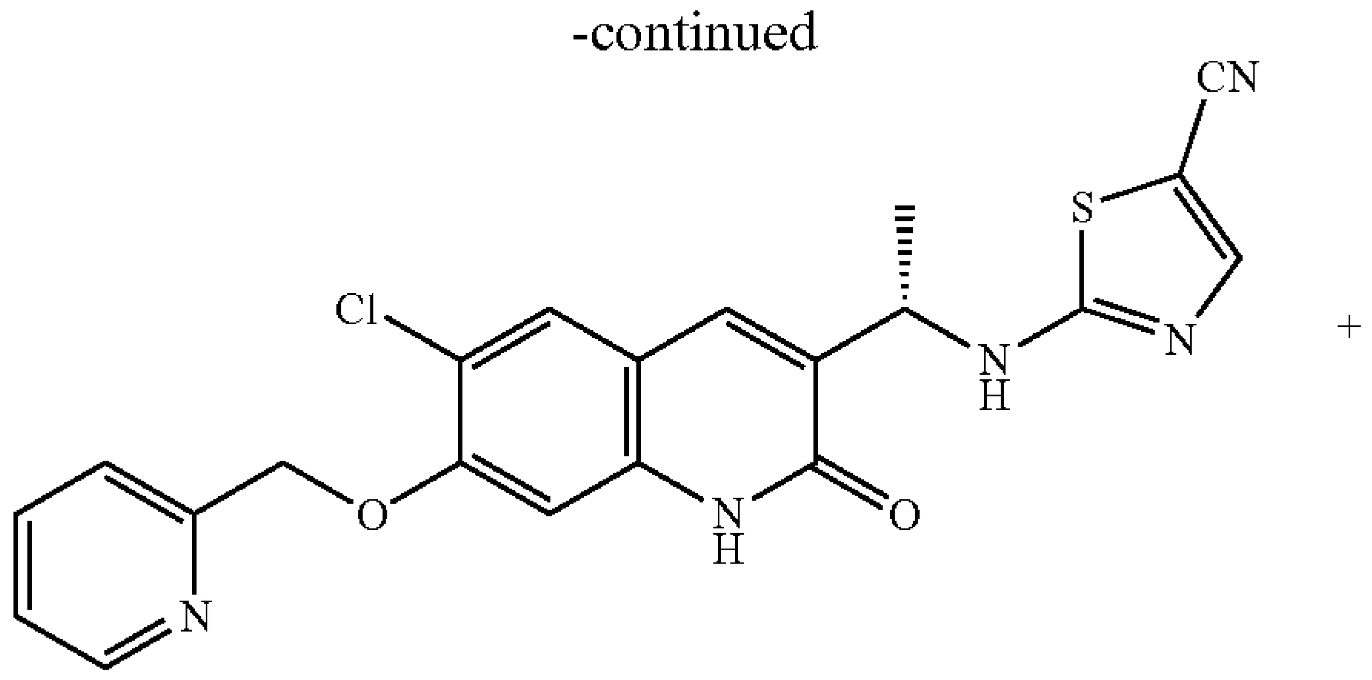
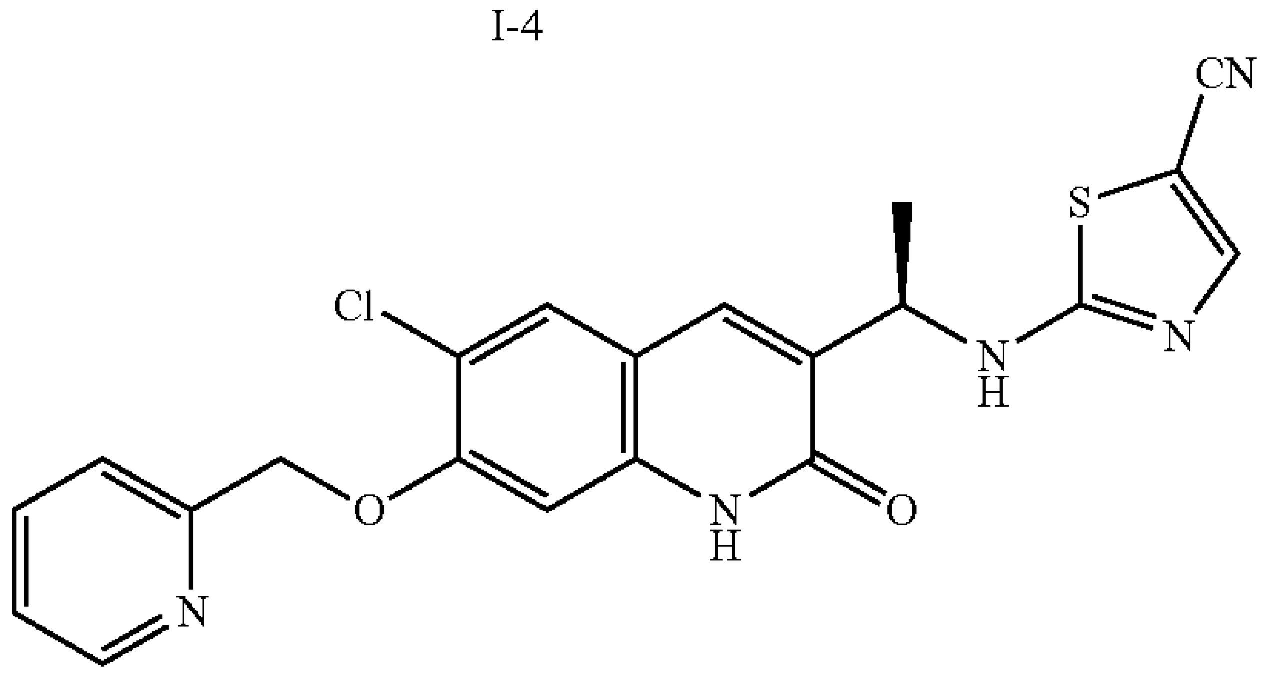


I-4



I-5

A mixture of 2-chlorothiazole-5-carbonitrile (33.1 mg, 0.229 mmol) and 3-(1-aminoethyl)-6-chloro-7-(pyridin-2-ylmethoxy)quinolin-2(1H)-one hydrochloride II-6 (74.9 mg, 0.205 mmol) was treated with DMSO (1.5 ml) and DIEA (108 μL, 0.618 mmol). The solution was stirred at 110° C. for 6.5 hours. The sample was mixed with water (30 mL) and extracted with DCM (2×15 mL). The extracts were dried (Na_2SO_4) and filtered, silica gel was added, and the solvent was evaporated under reduced pressure. The material was chromatographed by Biotage MPLC (10 g silica gel snap column) with 0 to 4% MeOH in DCM, with isocratic elution at 3.4% MeOH to provide 2-((1-(6-chloro-2-oxo-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-3-yl)ethyl)amino) thiazole-5-carbonitrile I-3 (52.1 mg, 0.119 mmol, 58.2% yield, HPLC purity 100% at 220 nm) as a solid. ^{1}H NMR (300 MHz, DMSO-d6): δ ppm 11.88 (s, 1H), 9.17 (br d, J=4.98 Hz, 1H), 8.58-8.63 (m, 1H), 7.83-7.92 (m, 3H), 7.71 (s, 1H), 7.55 (d, J=7.62 Hz, 1H), 7.38 (dd, J=6.89, 5.42 Hz, 1H), 7.03 (s, 1H), 5.30 (s, 2H), 4.85-5.00 (m, 1H), 1.44 (d, J=7.04 Hz, 3H). LCMS (Method 1): Rt 2.46 min., m/z 437.80 [M+H]+.

Chiral separation of the racemic mixture I-3 was performed to provide two pure enantiomers by using the following chiral HPLC condition:

Instrument: Gilson Prep HPLC
Column: CHIRALCEL OD-H, 2×25 cm, 5 um
Mobile phase: Hex:EtOH=85:15
Flow rate: 20 mL/min
Detector Wavelength: UV 220 nm
Sample Preparation: Racemate was dissolved in EtOH to 10.38 mg/ml
Injection Volume: 1 mL
Run Time per Injection: 18 min
Work Up: After separation, the fractions were dried off via rotary evaporator and then freeze dried.

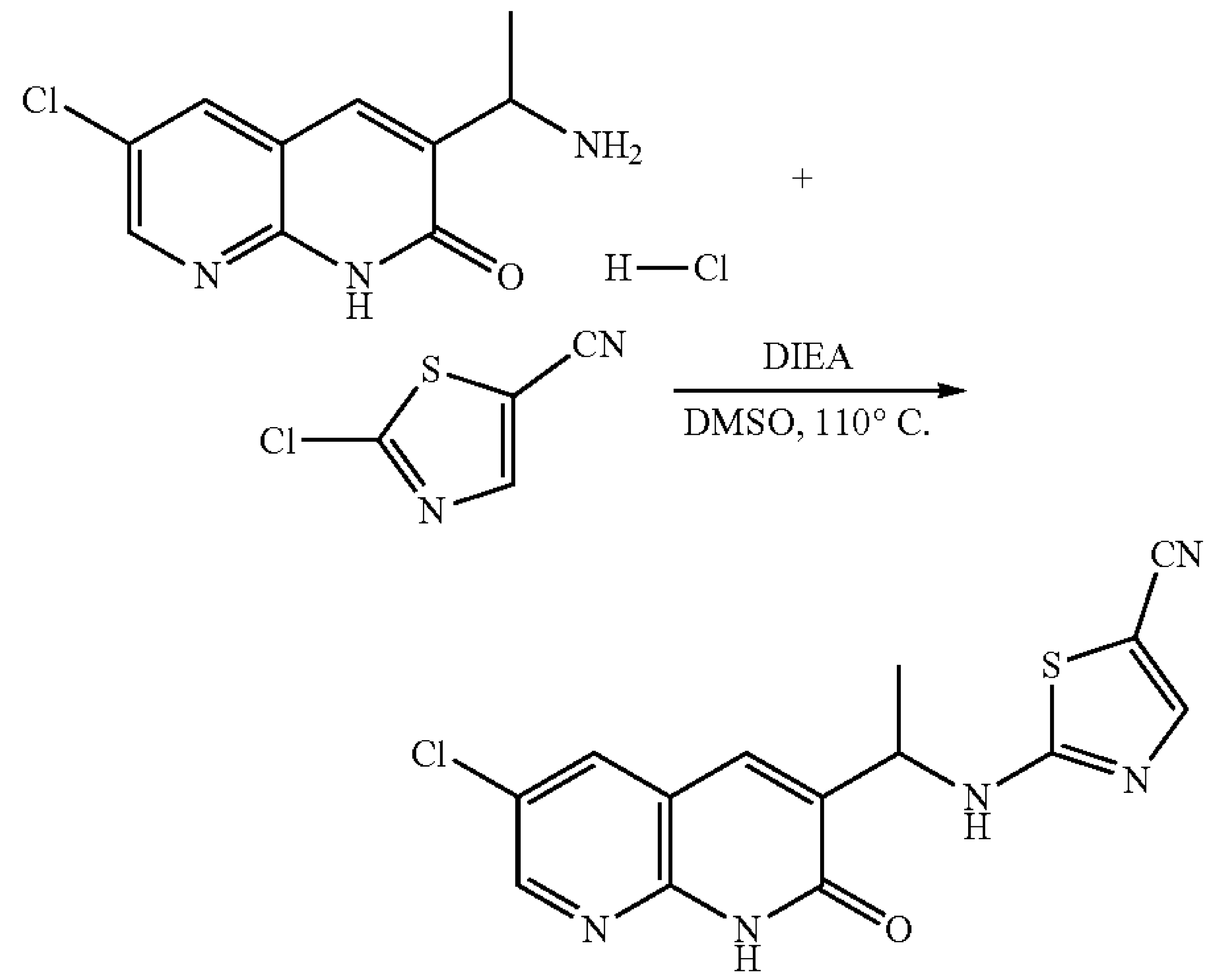
(S)-2-((1-(6-chloro-2-oxo-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-3-yl)ethyl)amino) thiazole-5-carbonitrile (I-4)

14.6 mg obtained, Chiral HPLC: Rt: 10.39 min, ee: >99%. LCMS (Method 4, at 220 nm): Rt 1.82 min., m/z 435.8 $[M+H]^+$.

(R)-2-((1-(6-chloro-2-oxo-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-3-yl)ethyl)amino) thiazole-5-carbonitrile (I-5)

14.9 mg obtained, Chiral HPLC: Rt: 12.98 min, ee: >99%. LCMS (Method 4, at 220 nm): Rt 1.82 min., m/z 435.8 $[M+H]^+$.

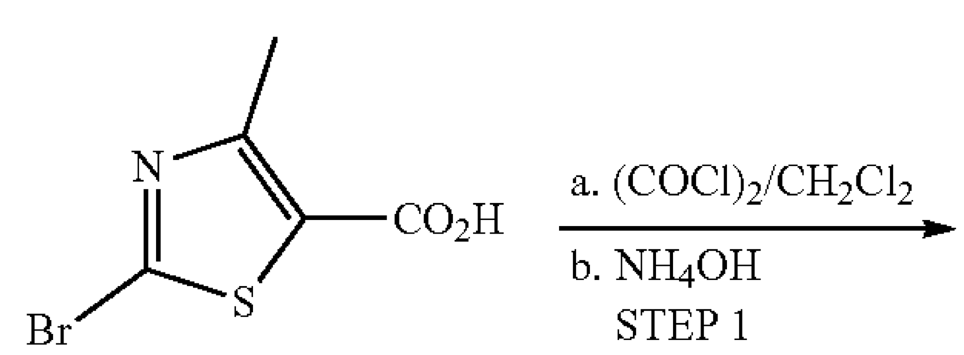
Example 18—2-((1-(6-chloro-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl)ethyl)amino)thiazole-5-carbonitrile (I-6)



I-6

A mixture of 2-chlorothiazole-5-carbonitrile (55.6 mg, 0.384 mmol) (Aldrich) and 3-(1-aminoethyl)-6-chloro-1,8-naphthyridin-2(1H)-one hydrochloride II-8 (100 mg, 0.384 mmol) was treated with DMSO (1.5 ml) and DIEA (0.201 ml, 1.153 mmol). The solution was stirred at 110° for 6.5 hours. The reaction mixture was cooled to room temperature, then water was added. The mixture was stirred at room temperature for 30 min. After filtration, the solid was purified by Biotag on a 25 g column with 10-98% EtOAC to afford 2-((1-(6-chloro-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl)ethyl)amino)thiazole-5-carbonitrile I-6 (55.6 mg, 43.6%): ^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 12.51 (s, 1H), 9.21 (d, J=6.74 Hz, 1H), 8.50 (d, J=2.35 Hz, 1H), 8.32 (d, J=2.64 Hz, 1H), 7.79 (s, 1H), 7.75 (s, 1H), 4.95 (m, 1H), 1.43 (d, J=6.74 Hz, 3H). LCMS (Method 1): Rt 2.08 min, m/z 332.00 $[M+H]^+$.

Example 19—((S)-2-((1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)amino)-4-methyl thiazole-5-carbonitrile (I-7)



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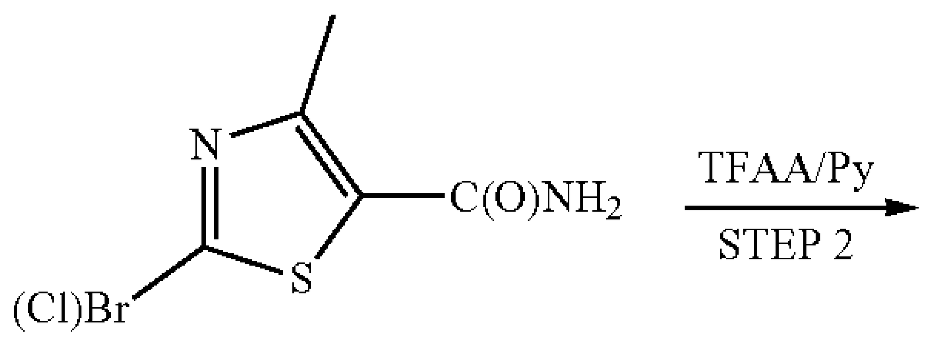
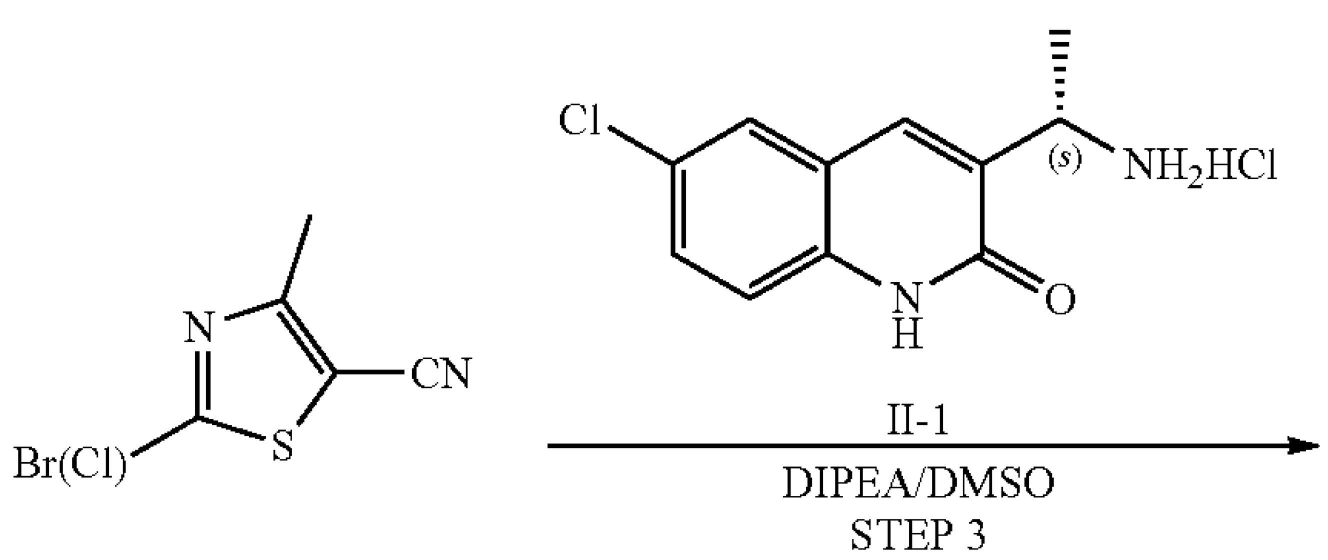
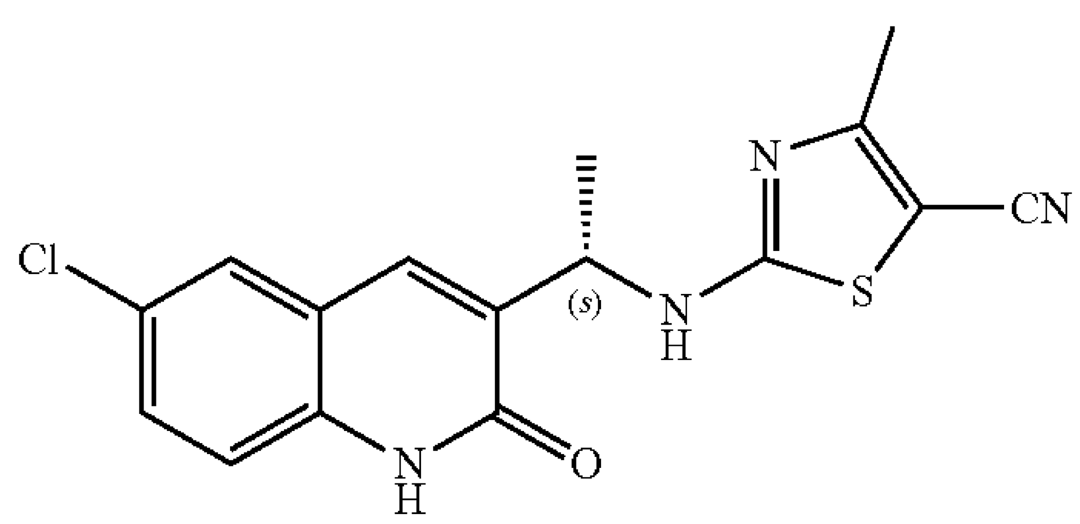


RCl:RBr = 2:1

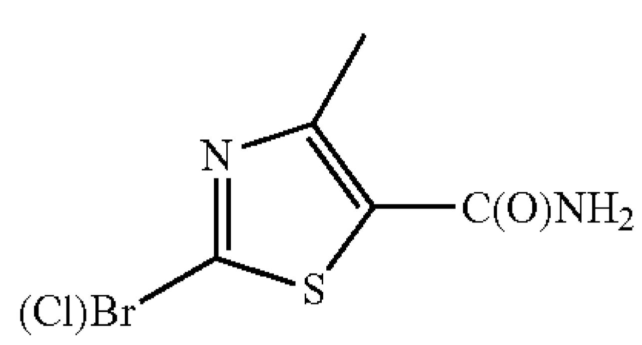


RCl:RBr = 2:1



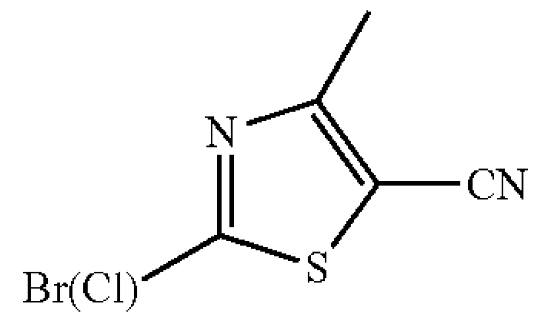
I-7

Step-1: 2-bromo(chloro)-4-methylthiazole-5-carboxamide



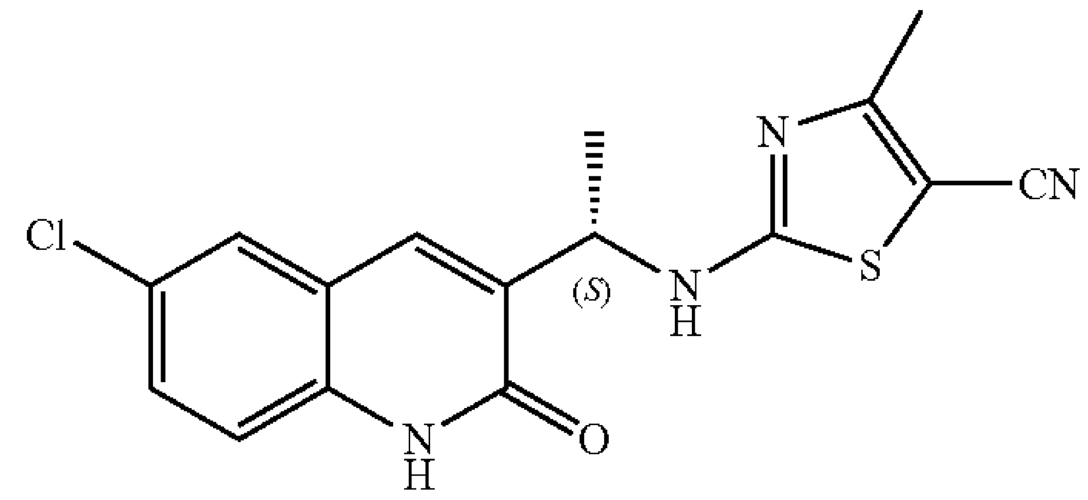
To an ice-cold suspension of 2-bromo-4-methylthiazole-5-carboxylic acid (0.6 g, 2.7 mmol) in dichloromethane was added neat oxalyl chloride (0.3 mL, 3.51 mmol) followed by an addition of 1 drop of DMF under N_2 flow. The reaction mixture was allowed to warm up slowly to room temperature (~over 4 h), then concentrated and kept under high vacuum line for 2h. The crude 2-bromo-4-methylthiazole-5-carbonyl chloride was dissolved in in 5 mL of dioxane and was added to 5 mL of ice-cold 14N NH_4OH. The reaction mixture was allowed to warm to room temperature overnight. Then the reaction mixture was diluted with dichloromethane and the layers were separated. Aqueous layer was extracted several times with CH_2Cl_2 and CH_2Cl_2-MeOH solvent mixture. Organic layers were combined, dried over Na_2SO_4, filtered and concentrated to dryness under reduced pressure. The crude (~0.5 g) was purified by ISCO, using 40 g normal phase column with a gradient elution of hexanes in EtOAc to afford 294 mg (57% yield) of the title mixture (Br:Cl=1:2).

Step-2: 2-chloro(bromo)-4-methylthiazole-5-carbonitrile



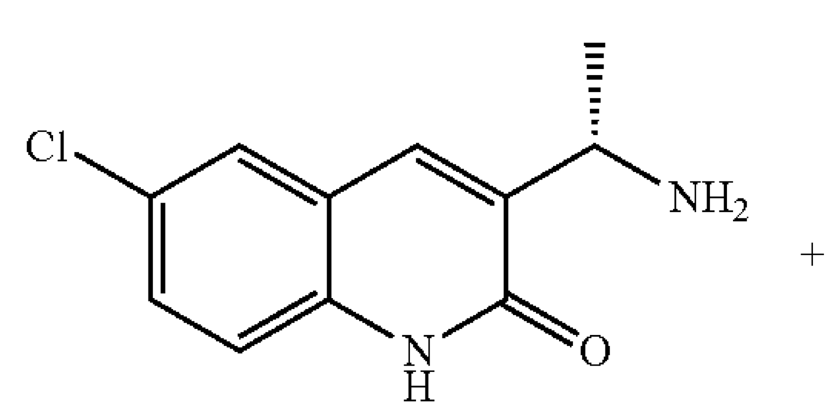
Neat TFAA (0.10 mL, 0.75 mmol) was added drop wise to an ice-cold solution of 2-bromo(chloro)-4-methylthiazole-5-carboxamide (100 mg. 0.52 mmol) in pyridine. The reaction mixture was allowed to warm up slowly to room temperature and then stirred at RT for 1 h. After the reaction was complete, it was quenched with water and extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, filtered and concentrated to dryness under reduced pressure. The crude was purified by ISCO, using 12 g normal phase column with a gradient elution of CH_2Cl_2 in EtOAc providing 69 mg (77% yield) of the mixture of the title compounds (Br:Cl=1:2).

Step-3: ((S)-2-((1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)amino)-4-methylthiazole-5-carbonitrile (I-7)



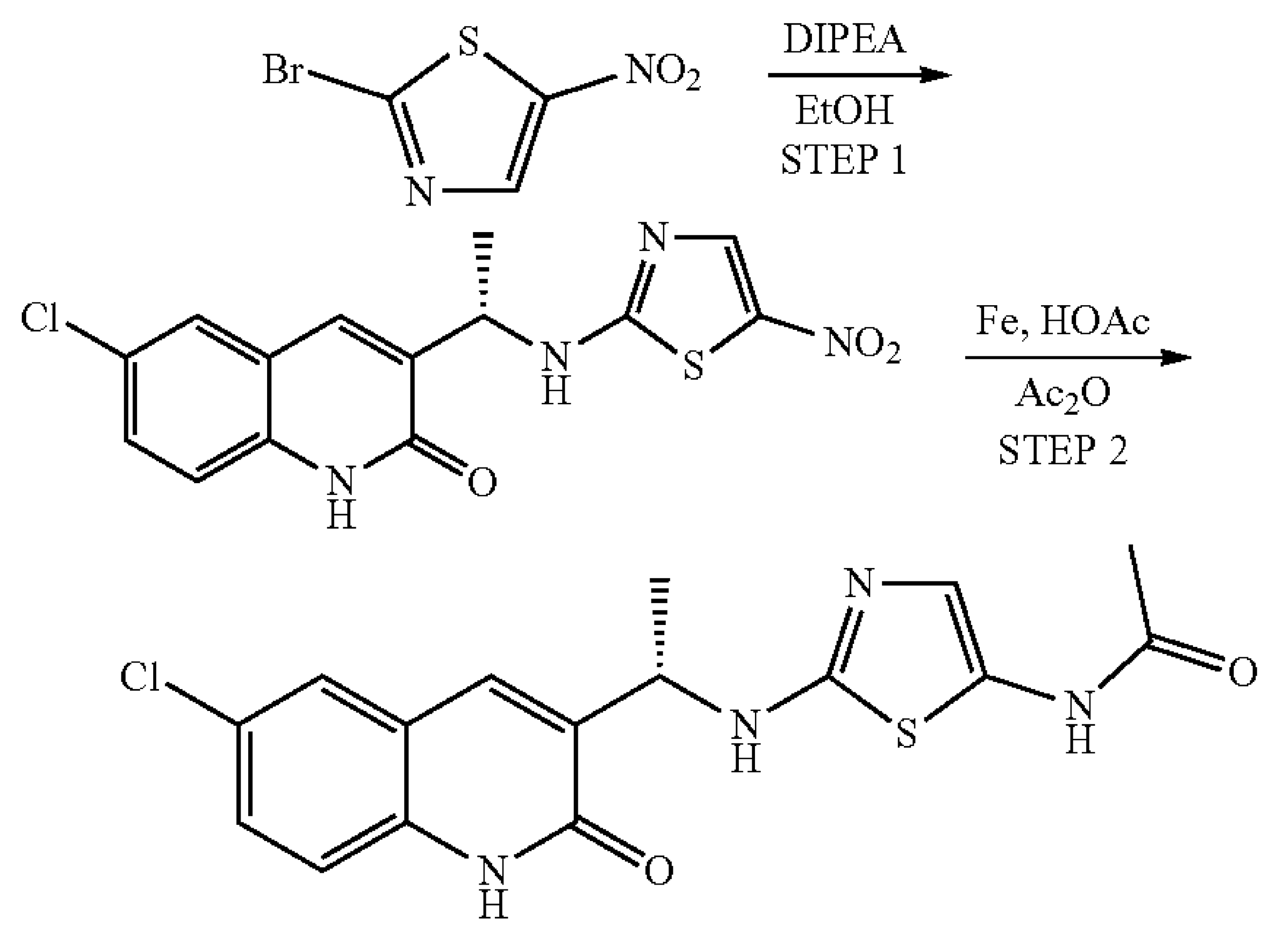
A mixture containing 2-chloro(bromo)-4-methylthiazole-5-carbonitrile (67 mg, 0.39 mmol), (S)-3-(1-aminoethyl)-6-chloroquinolin-2(1H)-one hydrochloride II-1 (150 mg, 0.58 mmol) and DIEA (0.24 mL, 1.2 mmol) in 2 mL of anhydrous DMSO was microwaved at 140° C. for 3 h. The reaction mixture was diluted with CH_2Cl_2 and washed with water, brine, dried over Na_2SO_4, filtered and concentrated to dryness under reduced pressure. The crude was purified by ISCO, using 12 g normal phase "gold" column with a gradient elution of EtOAc in CH_2Cl_2, providing 81 mg (73% yield) of the title compound. ^{1}H NMR (300 MHz, DMSO-d6): δ ppm: 12.06 (br s 1H), 9.11 (br s, 1H), 8.82 (d, J=2.2 Hz, 1H), 7.77 (s, 1H), 7.53 (dd, J_1=8.8 Hz, J_2=2.2 Hz, 1H), 7.31 (d, J=8.8 Hz, 1H), 4.90-5.00 (m, 1H), 2.23 (s, 3H), 1.44 (d, J=6.6 Hz, 3H). LCMS (Method 3): Rt 5.11 min. m/z 345.1 $[M+H]^+$.

Example 20—(S)—N-(2-((1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)amino)thiazol-5-yl) acetamide (I-8)



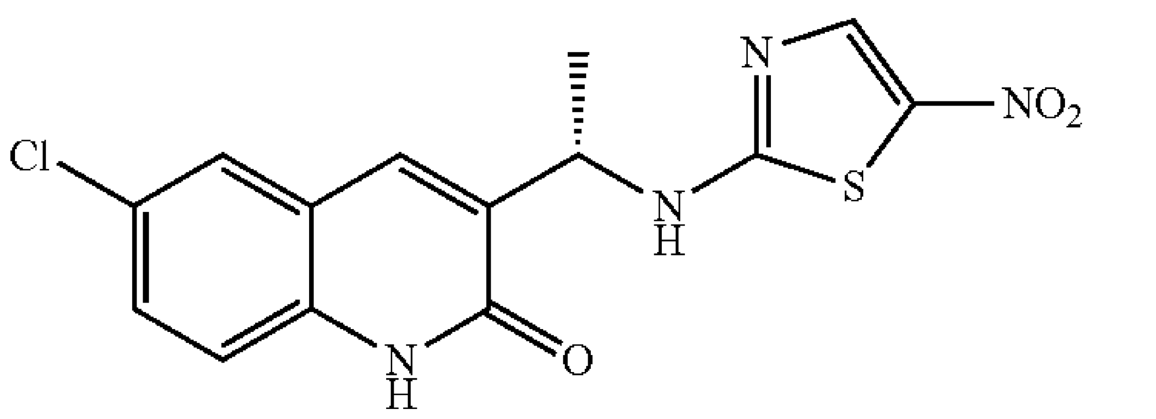
II-1

-continued



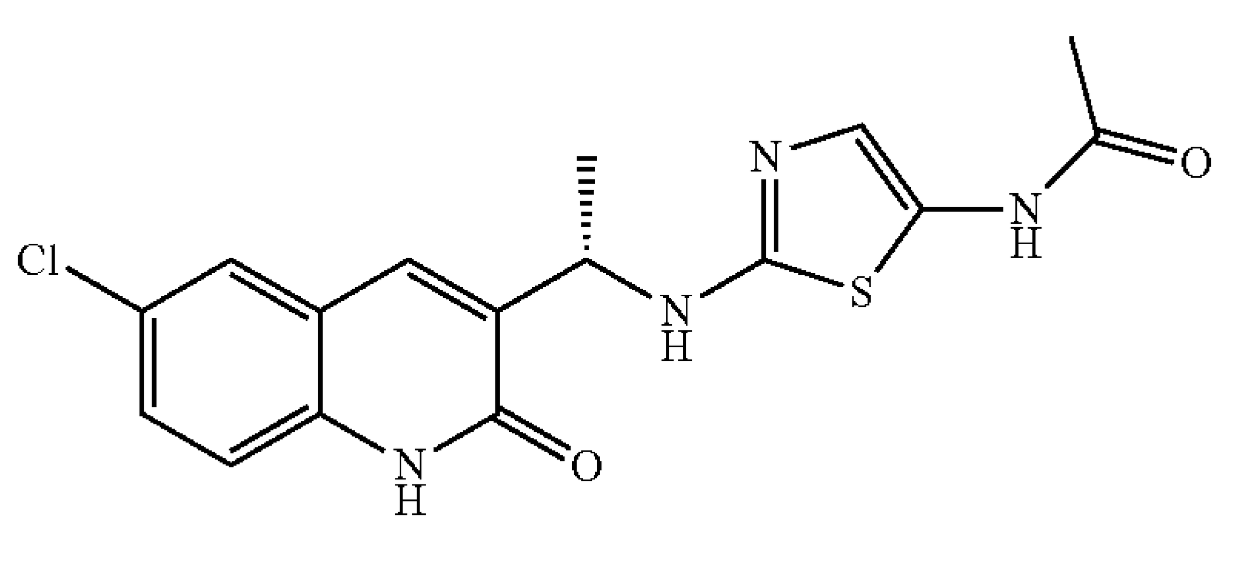
I-8

Step-1: (S)-6-Chloro-3-(1-((5-nitrothiazol-2-yl) amino)ethyl)quinolin-2(1H)-one



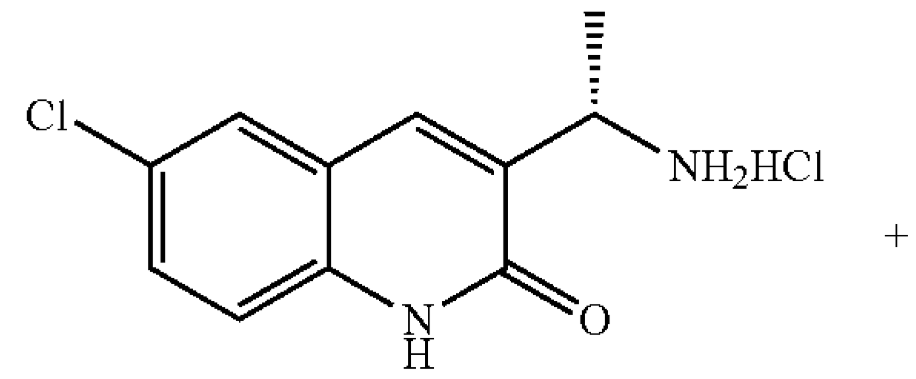
In a sealed tube, a mixture of (S)-3-(1-aminoethyl)-6-chloroquinolin-2(1H)-one (II-1 free base, 410 mg, 1.8 mmol, 1 eq.), 2-bromo-5-nitrothiazole (1, 418 mg, 2 mmol, 1.1 eq.) and DIPEA (519 mg, 4 mmol, 2.2 eq.) in 5 mL EtOH was heated at 85° C. for 30 minutes. The reaction was then poured into water and extracted with EtOAc (2×). After drying over Na_2SO_4, the crude extract was chromatographed over 20 g silica gel, eluting with DCM/2% EtOH to provide 289 mg 2 (46%).

Step-2: (S)—N-(2-((1-(6-chloro-2-oxo-1,2-dihydro-quinolin-3-yl)ethyl)amino)thiazol-5-yl) acetamide (I-8)

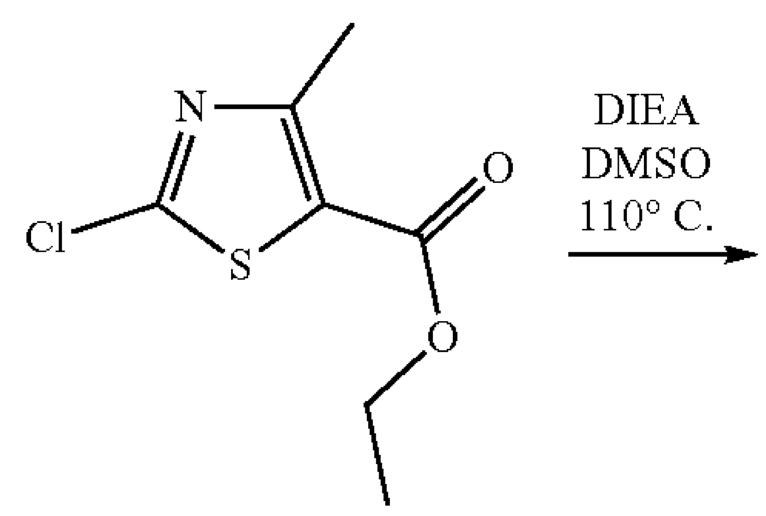


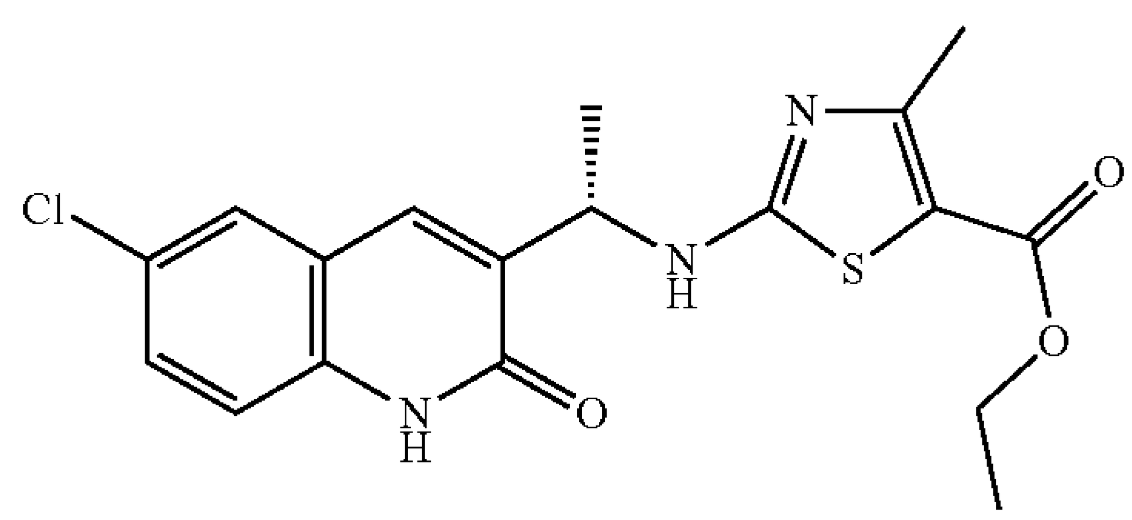
A suspension of (S)-6-chloro-3-(1-((5-nitrothiazol-2-yl) amino)ethyl)quinolin-2(1H)-one, (289 mg, 0.82 mmol, 1 eq.) in 5.5 mL HOAc was treated with iron (~325 mesh, 289 mg, 5.17 mmol, 6.3 eq.) and acetic anhydride (125 mg, 1.2 mmol, 1.5 eq.). After 50 minutes heating at 85° C., the reaction was diluted with ice water and then neutralized with aqueous $NaHCO_3$. Following extraction with EtOAc (2×) and drying over Na_2SO_4, the crude extract was filtered through celite. Chromatography over 4 g silica gel, eluting with a DCM to DCM/10% EtOH gradient, followed by trituration with Et_2O/DCM, afforded 105 mg I-8 as a beige solid (35%). ^{1}H-NMR (300 MHz, d_6DMSO) δ ppm: 11.97 (s, 0.8H), 10.58 (s, 1H), 7.75 (s, 1H), 7.72 (s, 1H), 7.60 (d, J=6.6, 1H), 7.47 (d, J=8.25, 1H), 7.28 (d, J=8.79, 1H), 6.61 (s, 1H), 4.84 (m, 1H), 1.90 (s, 3H), 1.36 (d, J=6.60, 3H). LC/MS (Methods 3), Rt 3.9 min., m/z 363 [M+H]$^+$.

Example 21—(5)-ethyl 2-((1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)amino)-4-methylthiazole-5-carboxylate (I-9)



II-1

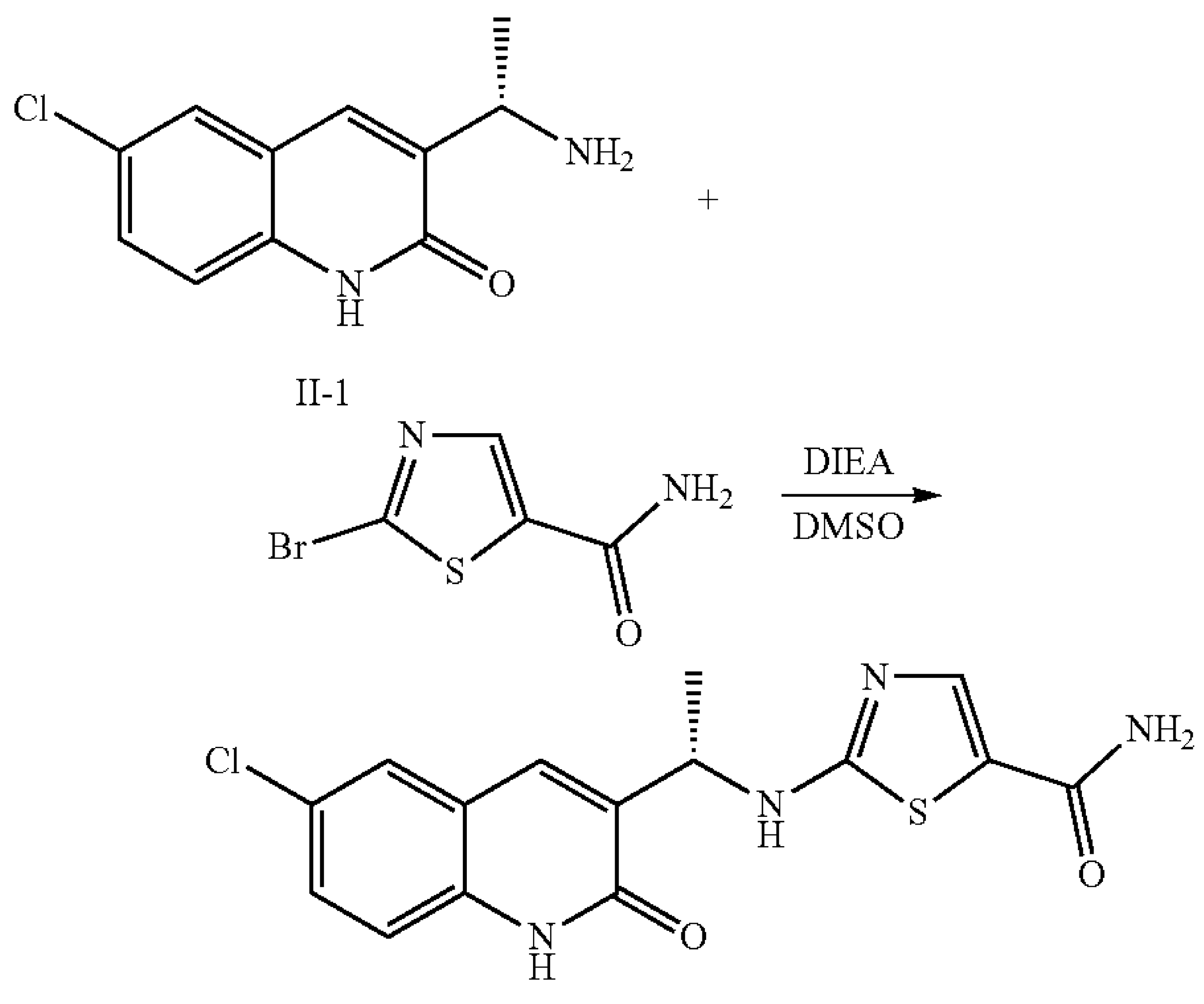




I-9

A mixture of ethyl 2-chloro-4-methylthiazole-5-carboxylate (79 mg, 0.386 mmol) and (S)-3-(1-aminoethyl)-6-chloroquinolin-2(1H)-one hydrochloride II-1 (100 mg, 0.386 mmol) was treated with DMSO (1.0 ml) and DIEA (0.20 ml, 1.145 mmol). The solution was stirred at 110° C. for seven hours. The sample was mixed with water (15 mL) and extracted with DCM (2×15 mL). The extract was dried (Na2SO4) and filtered, silica gel was added, and the solvent was evaporated under reduced pressure. The material was chromatographed by Biotage MPLC (10 g silica gel snap column) with 0 to 55% EtOAc in hexanes, with isocratic elution at 55% EtOAc to provide (S)-ethyl 2-((1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)amino)-4-methylthiazole-5-carboxylate (102.8 mg, 0.262 mmol, 68% yield, HPLC purity 100% at 220 nm) as a yellow brittle foam. ^{1}H NMR (300 MHz, DMSO-d6): δ ppm 12.05 (s, 1H), 8.86 (br d, J=7.33 Hz, 1H), 7.82 (d, J=2.35 Hz, 1H), 7.76 (s, 1H), 7.52 (dd, J=8.79, 2.35 Hz, 1H), 7.31 (d, J=8.79 Hz, 1H), 4.78-4.96 (m, 1H), 4.08-4.17 (m, 2H), 2.37 (s, 3H), 1.43 (d, J=6.74 Hz, 3H), 1.20 (t, J=7.04 Hz, 3H). LCMS (Method 1): Rt 2.48 min., m/z 391.88 [M+H]$^+$.

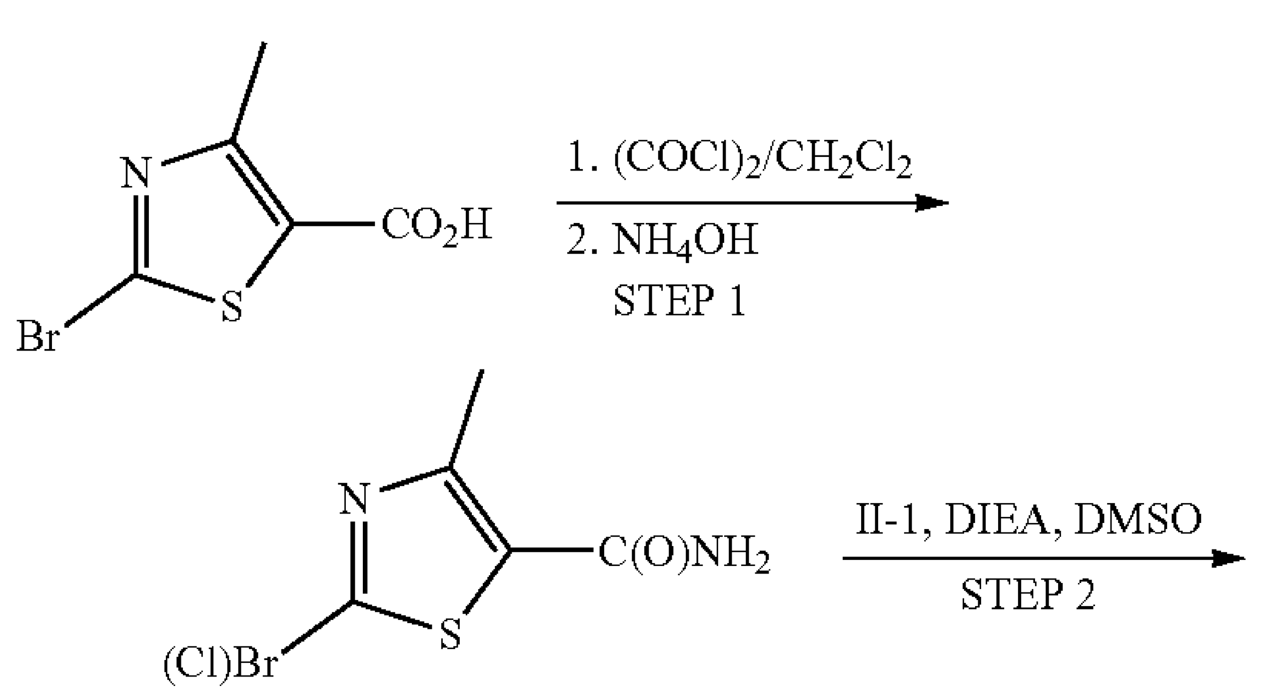
Example 22—(S)-2-((1-(6-Chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)amino)thiazole-5-carboxamide (I-10)



I-10

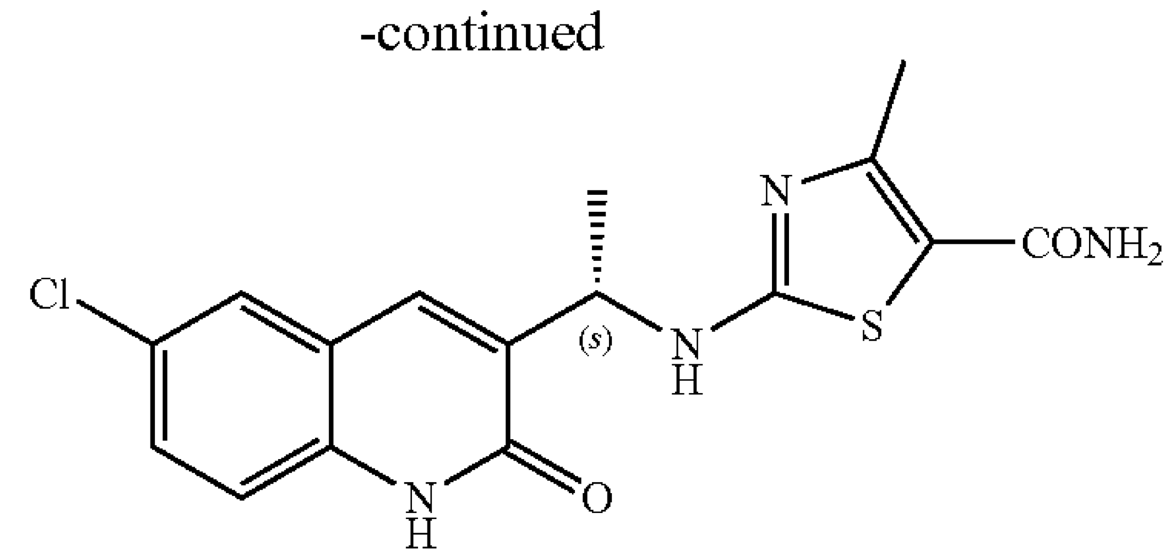
A mixture of (S)-3-(1-aminoethyl)-6-chloroquinolin-2(1H)-one HCl, II-1 (450 mg, 1.7 mmol, 1 eq.), 2-bromothiazole-5-carboxamide (425 mg, 2.05 mmol, 1.2 eq.) and DIEA (482 mg, 3.7 mmol, 2.2 eq.) in 10 mL DMSO in a sealed tube was heated at 140° C. for 2.5 hours. The reaction was then poured into water and extracted with EtOAc (×2). The combined organic extracts were washed with brine and dried over Na_2SO_4. After rotary evaporation, trituration with DCM afforded 184 mg crude product as a solid. Chromatography over 6.5 g silica gel, eluting with a 0 to 15% EtOH/DCM gradient, provided 100 mg of crude product as a gold solid still containing DIEA. Trituration with DCM, followed by evaporation of a MeOH solution of the solid afforded 70 mg I-10 as a yellow-orange solid (10%). ^{1}H-NMR (300 MHz, d_6DMSO) δ ppm: 12.0 (s, 0.75H), 8.54 (d, J=6.87, 1H), 7.79 (d, J=2.19, 1H), 7.73 (s, 1H), 7.61 (s, 1H), 7.61 (broad s, 1H), 7.48 (dd, J=2.19, 8.79, 1H), 7.29 (d, J=8.79, 1H), 7.06 (broad s, 1H), 4.89 (m, 1H), 1.40 (d, J=6.60, 3H). LCMS (Method 3): Rt 3.85 min, m/z 349 $[M+H]^+$.

Example 23—(S)-2-((1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)amino)-4-methylthiazole-5-carboxamide (I-11)



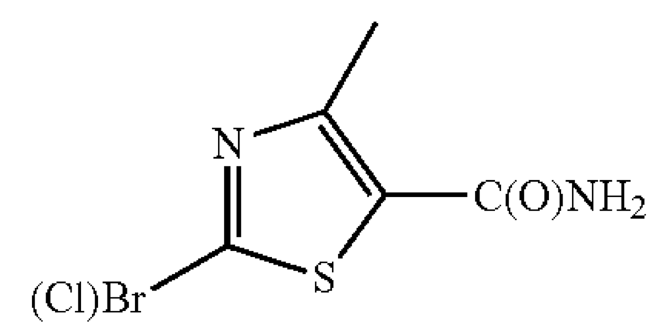
RCl:RBr = 2:1

-continued



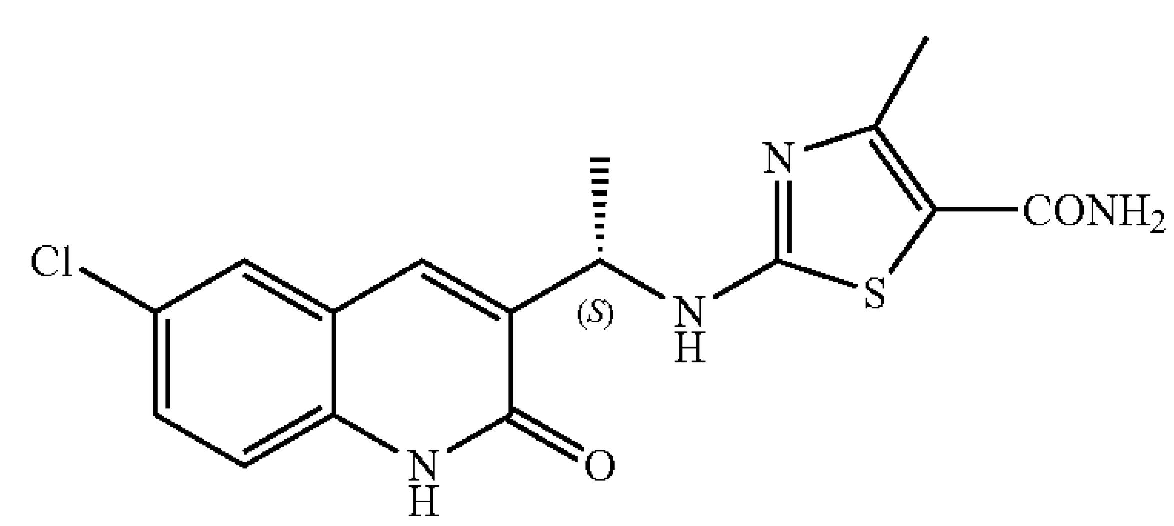
I-11

Step-1: 2-bromo(chloro)-4-methylthiazole-5-carboxamide



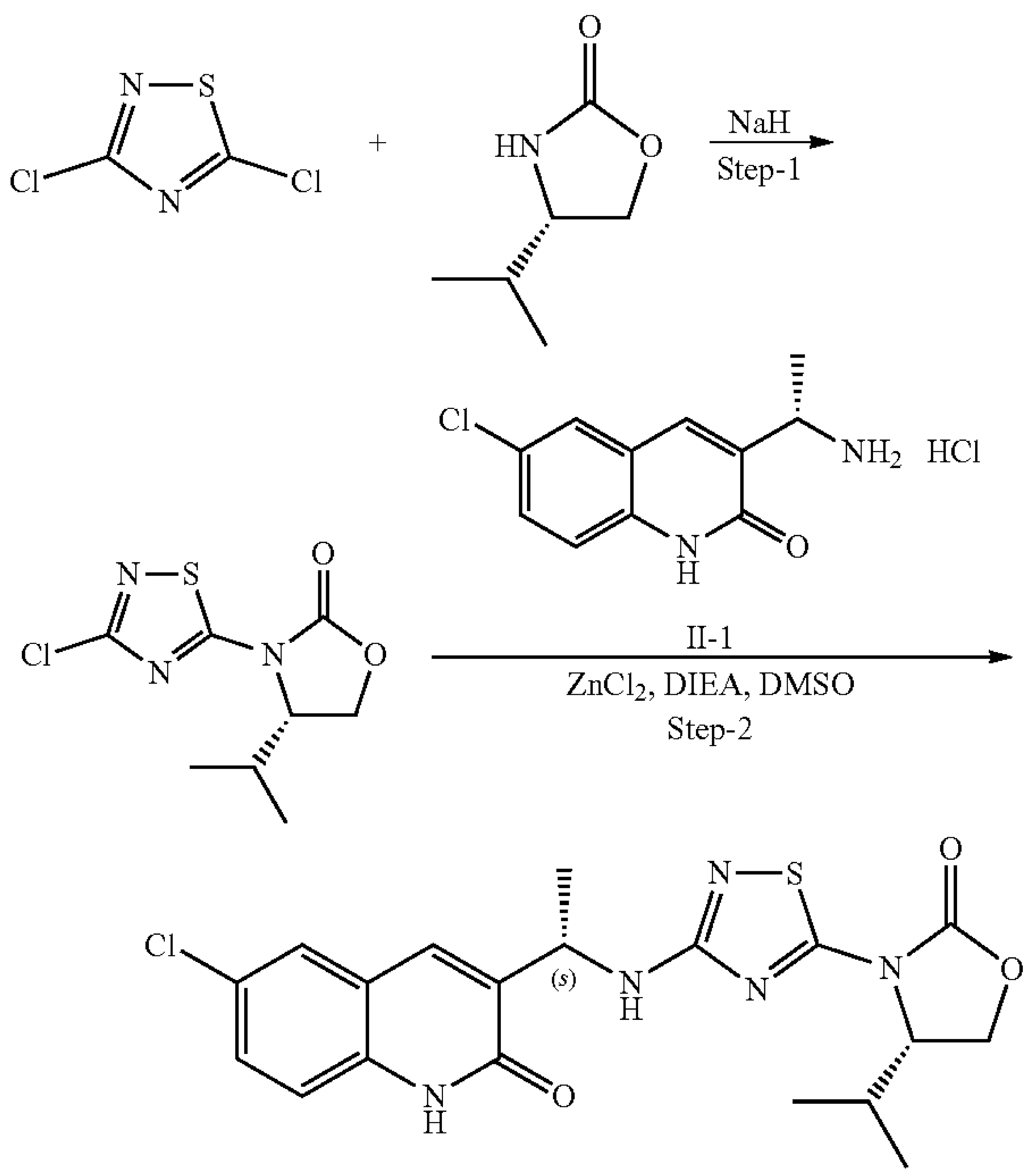
To an ice-cold suspension of 2-bromo-4-methylthiazole-5-carboxylic acid (0.6 g, 2.7 mmol) in dichloromethane was added neat oxalyl chloride (0.3 mL, 3.51 mmol) followed by an addition of 1 drop of DMF under N_2 flow. The reaction mixture was allowed slowly to warm to room temperature (~over 4 h), then concentrated and kept under high vacuum line for 2 h. The crude 2-bromo-4-methylthiazole-5-carbonyl chloride was dissolved in in 5 mL of dioxane and added to 5 mL of ice-cold 14N NH_4OH. The reaction mixture was allowed to warm to room temperature overnight. Then the reaction mixture was diluted with dichloromethane and the layers were separated. Aqueous layer was extracted several times with CH_2Cl_2 and CH_2Cl_2-MeOH solvent mixture. Organic layers were combined, dried over Na_2SO_4, filtered and concentrated to dryness under reduced pressure. The crude (~0.5 g) was purified by ISCO, using 40 g normal phase column with a gradient elution of Hexanes in EtOAc providing 294 mg (57% yield) of the title compound as a mixture (Br:Cl=1:2).

Step-2: (S)-2-((1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)amino)-4-methylthiazole-5-carboxamide (I-11)



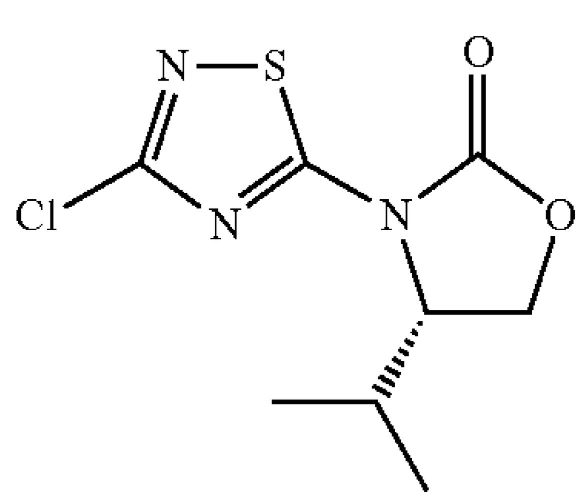
A mixture containing 2-bromo(chloro)-4-methylthiazole-5-carboxamide (360 mg, 1.9 mmol), (S)-3-(1-aminoethyl)-6-chloroquinolin-2(1H)-one hydrochloride II-1 (550 mg, 2.1 mmol) and DIEA (0.95 mL, 4.9 mmol) in 8 mL of anhydrous DMSO in a sealed tube was stirred at 140° C. for 2 h 30 min. The reaction mixture was diluted with CH_2Cl_2 and washed with water, brine, dried over Na_2SO_4, filtered and concentrated to dryness under reduced pressure. The crude was purified by ISCO, using 40 g normal phase "gold" column with a gradient elution of EtOAc in CH_2Cl_2, providing 100 mg (15% yield) of the title compound. ^1H NMR (300 MHz, DMSO-d_6): δ ppm: 12.02 (br s 1H), 8.45 (d, J=6.8 Hz, 1H), 7.8 (d, J=2.2 Hz, 1H), 7.74 (s, 1H), 7.52 (dd, J_1=8.8 Hz, J_2=2.2 Hz, 1H), 7.31 (d, J=6.6, 1H), 6.95 (d, J=8.8 Hz, 2H), 4.80-4.90 (quintet, 1H), 2.33 (s, 3H), 1.40 (d, J=6.6, 3H). LCMS (Method 3), Rt 3.82 min, m/z 363.1 $[M+H]^+$.

Example 24—(S)-2-((1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)amino)-4-methylthiazole-5-carboxamide (I-12)



I-12

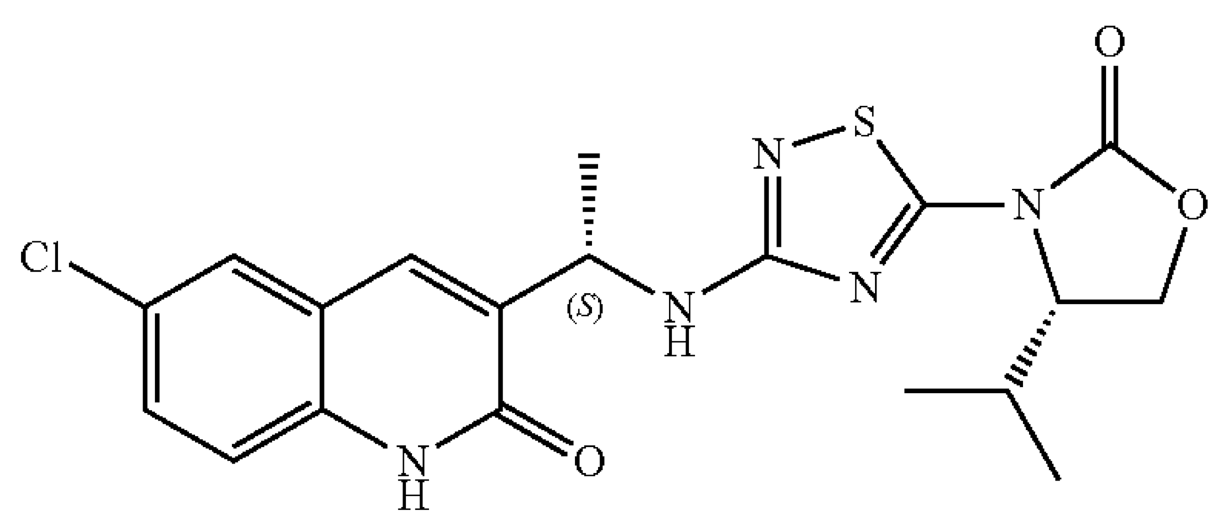
Step-1: (S)-3-(3-chloro-1,2,4-thiadiazol-5-yl)-4-isopropyloxazolidin-2-one



In a 50 mL round-bottomed flask was added (S)-4-isopropyloxazolidin-2-one (0.437 g, 3.39 mmol) in anhydrous THF (6 ml) at 0° C. in an ice bath. NaH (0.155 g, 3.87 mmol) was added portion wise and the resultant suspension was stirred at RT for 1 hour. The suspension was cooled in an ice-bath and 3,5-dichloro-1,2,4-thiadiazole (0.5 g, 3.23 mmol) was added portionwise. The reaction mixture was stirred at RT overnight. The solvent was removed under

reduced pressure and the resultant material was partitioned between ethyl acetate and saturated. Na_2CO_3. The aqueous layer was extracted with ethyl acetate and the combined organics were washed with brine (1×), dried over Na_2SO_4, filtered and concentrated under reduced pressure to give white solids. This crude was purified by normal column chromatography (0-10% EtOAc in hexanes) to give a pure product (489 mg, 61% yield). ^1H NMR (300 MHz, DMSO-d_6): δ ppm: 4.67-4.48 (m, 4H), 2.85 (m, 1H), 1.02 (d, J=6.9 Hz, 3H), 1.02 (d, J=7.2 Hz, 3H). LCMS (Method 1), Rt 2.22 min, m/z 247.95 $[M+H]^+$.

Step-2: (S)-3-(3-(((S)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl)amino)-1,2,4-thiadiazol-5-yl)-4-isopropyloxazolidin-2-one (I-12)



A mixture of (S)-3-(1-aminoethyl)-6-chloroquinolin-2(1H)-one hydrochloride II-1 (50 mg, 0.193 mmol), 3-(3-chloro-1,2,4-thiadiazol-5-yl)oxazolidin-2-one (39.7 mg, 0.193 mmol), DIEA (0.168 mL, 0.965 mmol) and zinc(II) chloride (39.4 mg, 0.289 mmol) was placed under nitrogen in a Microwave tube. The mixture was stirred in a Microwave apparatus at 140° C. for 2 h. LCMS showed many by-product was formed, only 10% desired product was formed. The reaction mixture was diluted with EtOAc and washed with water (×1), then brine (×2). The organic was concentrated and subjected a column chromatography on Biotage to afford 1.9 mg of desired product with ~80% HPLC purity. This impure material was further purified by reverse phase HPLC to yield 0.6 mg of the desired product I-12: LCMS (Method 1), Rt 2.57 min, m/z 391.94$[M+H]^+$.

TABLE 2

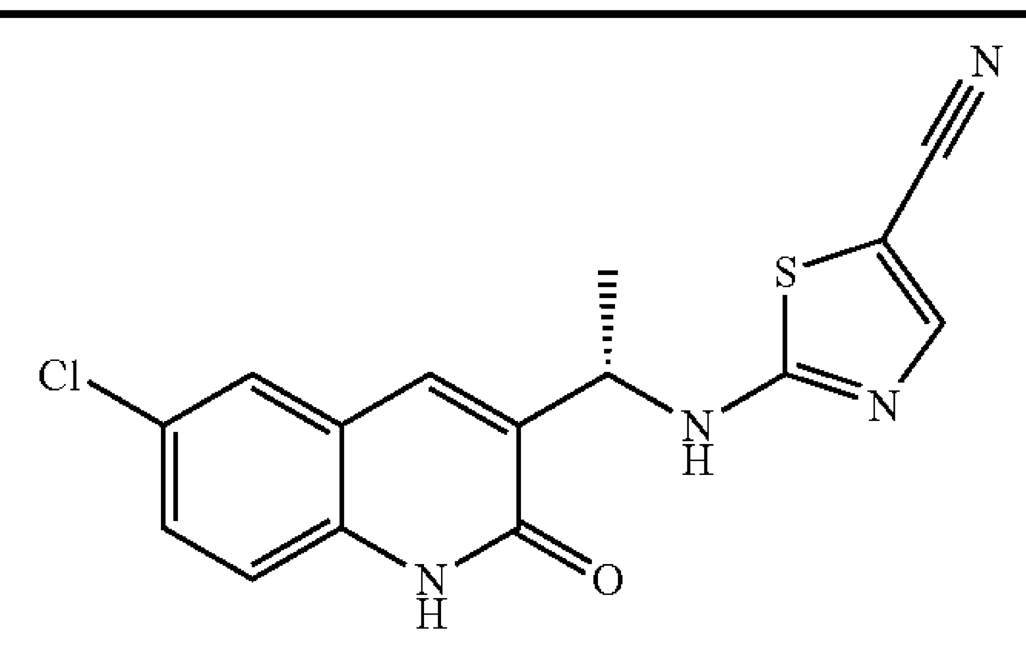
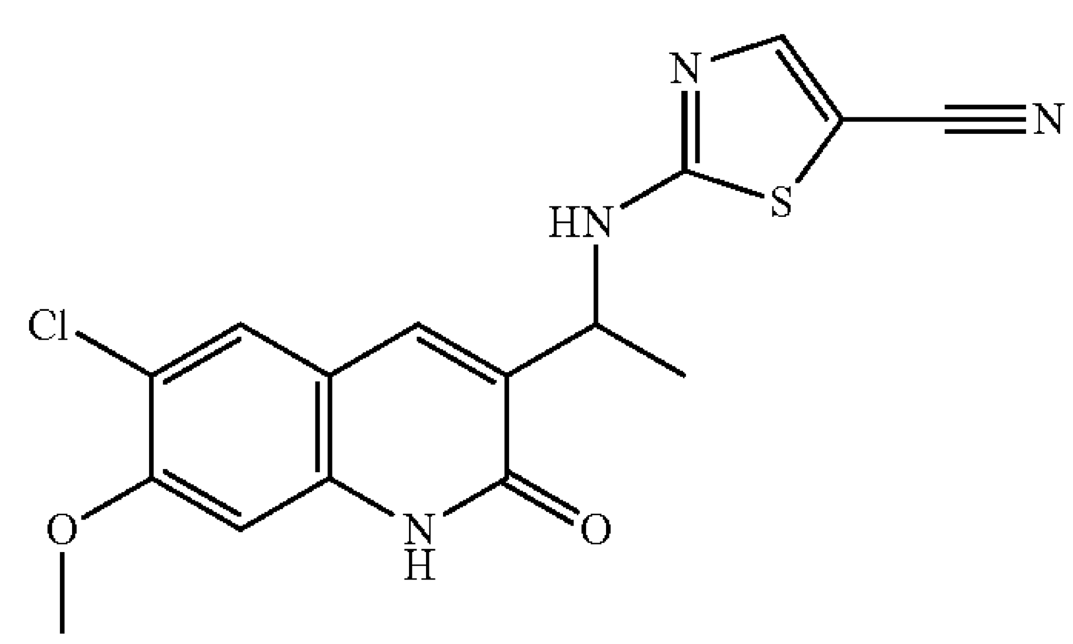
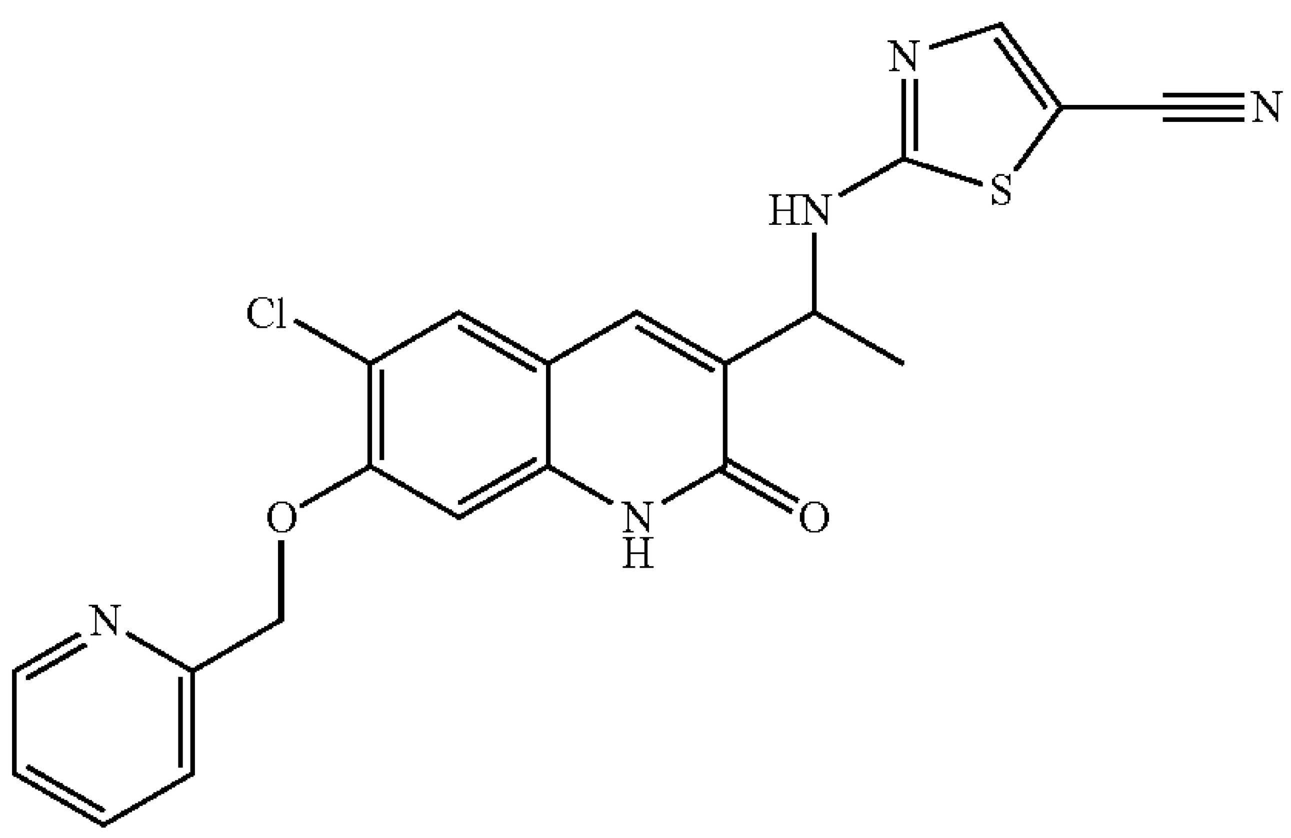
The structures of compound I-1 to I-12	
	I-1
	I-2

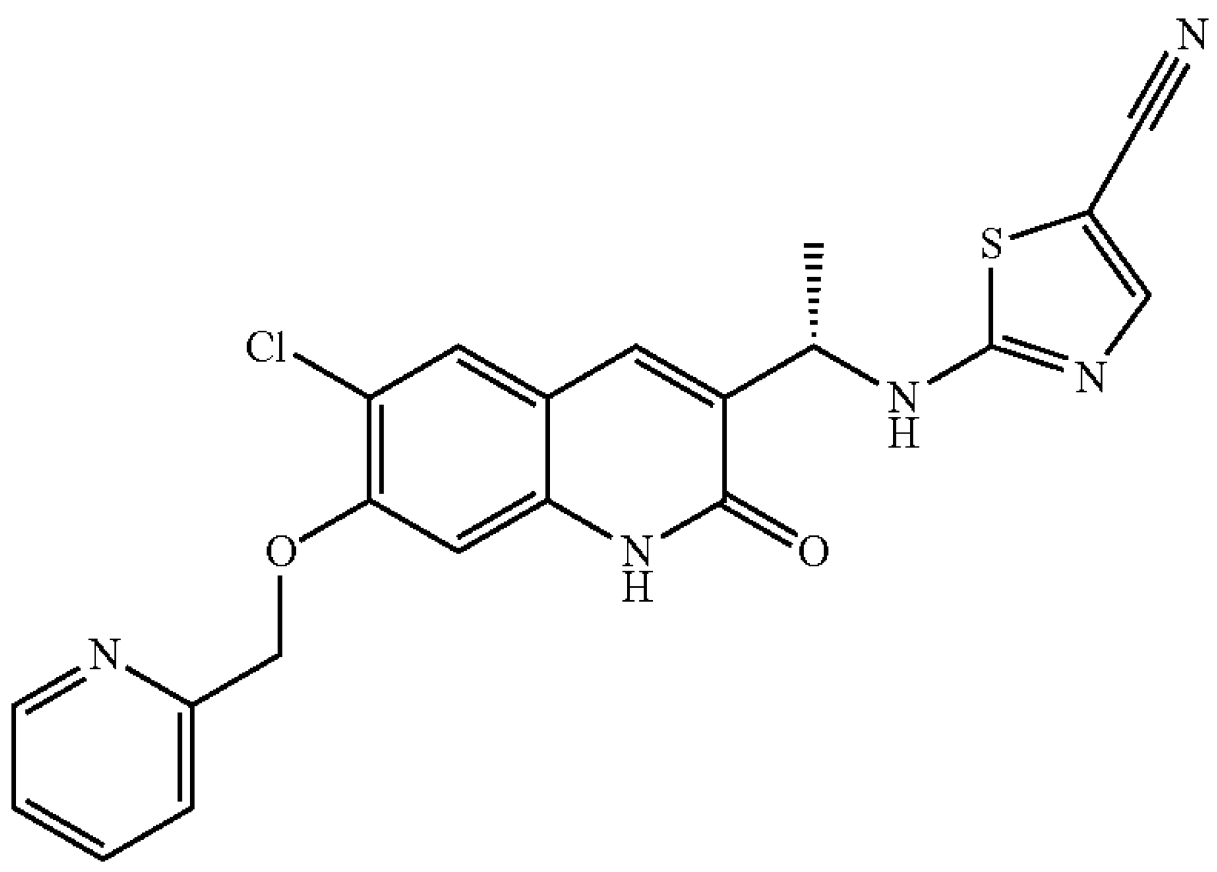
TABLE 2-continued

The structures of compound I-1 to I-12

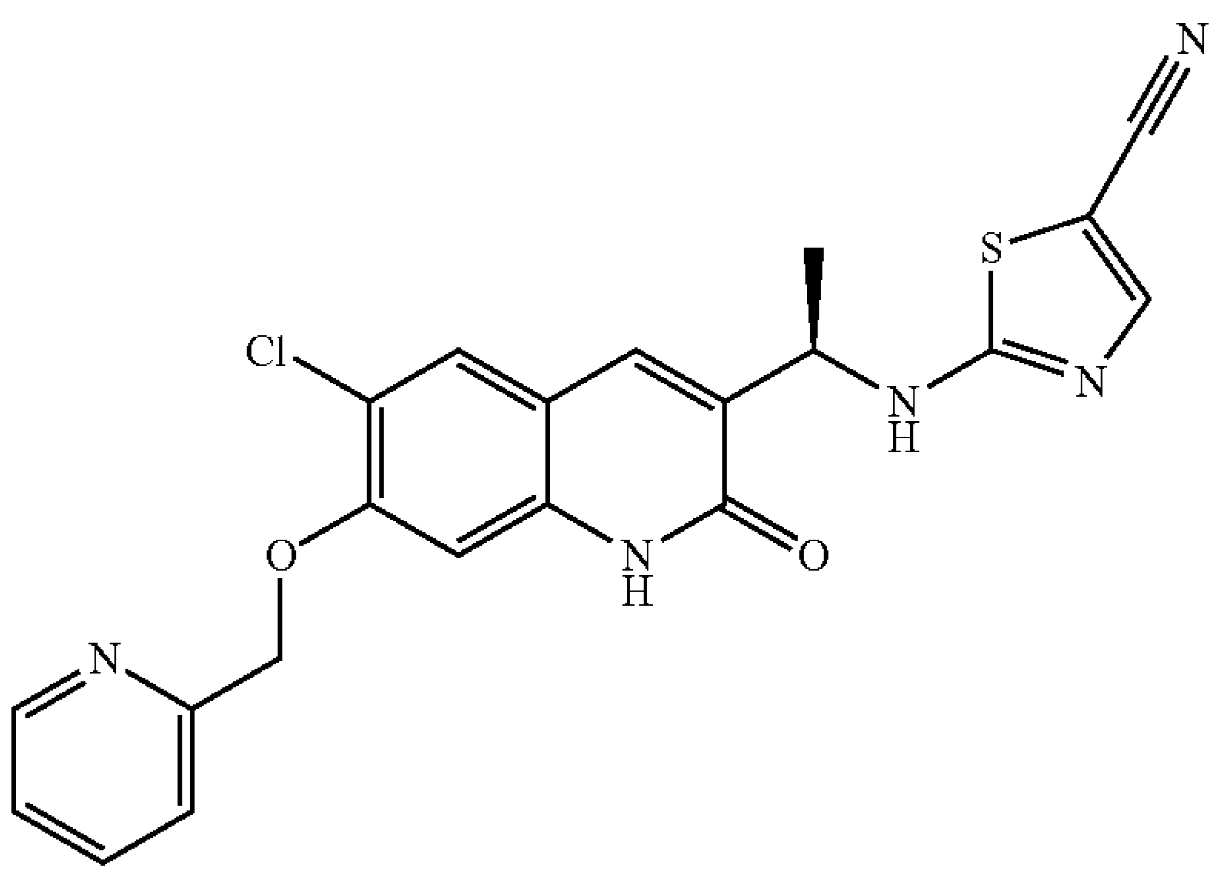
I-3



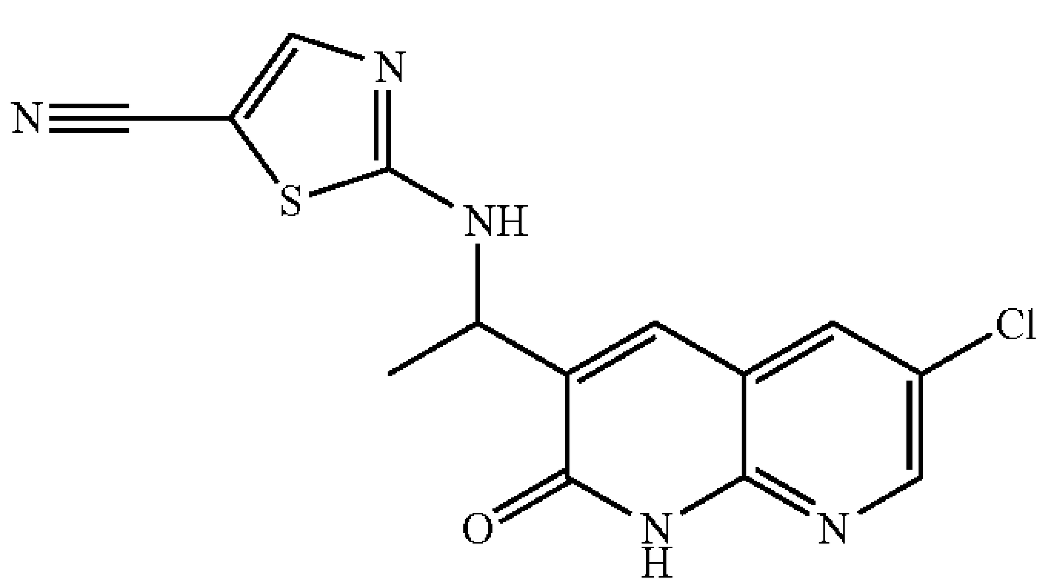
I-4



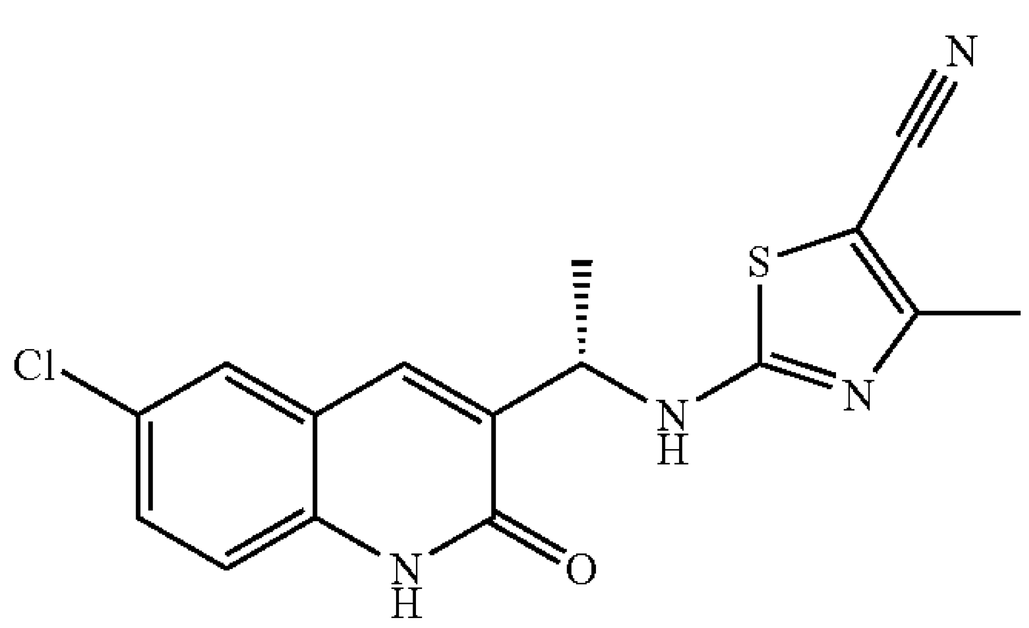
I-5



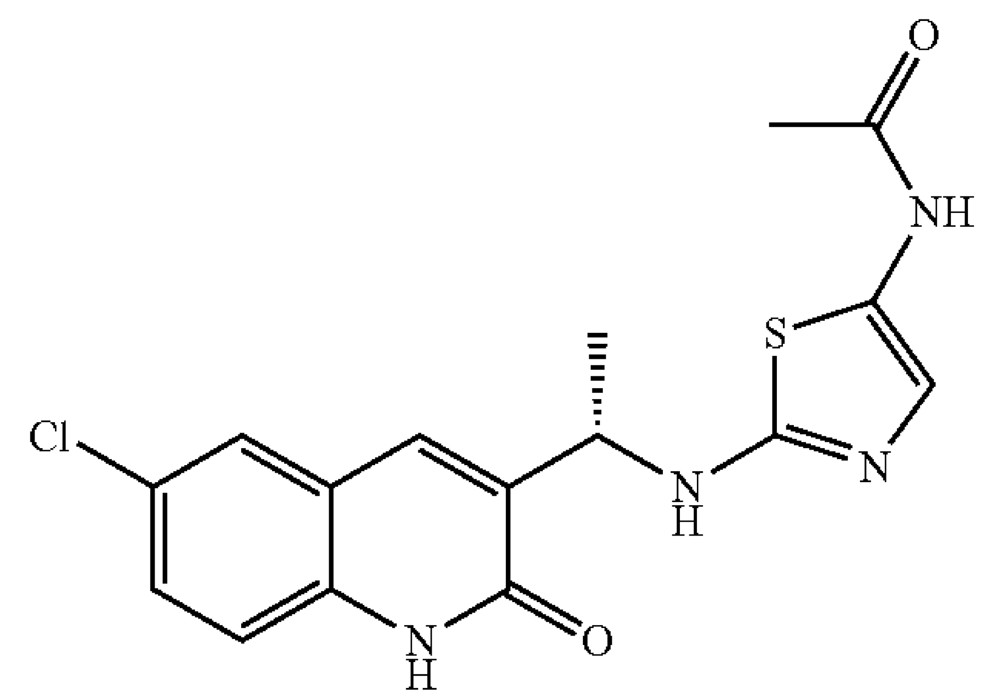
I-6



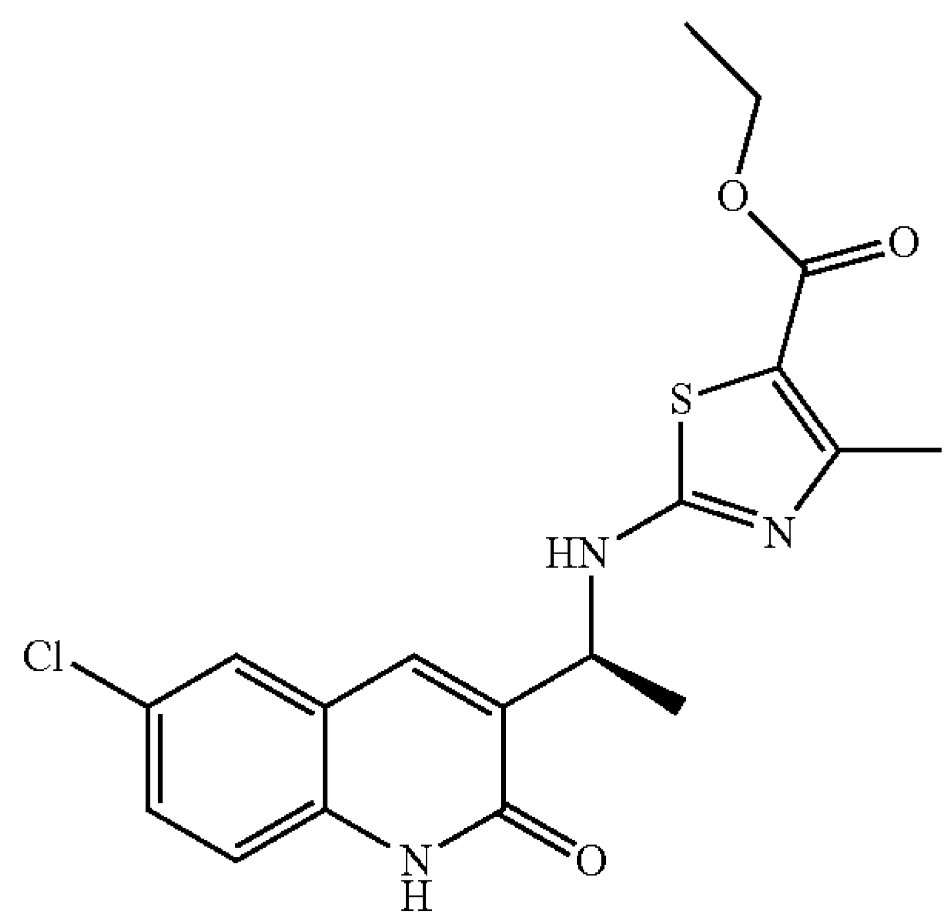
I-7



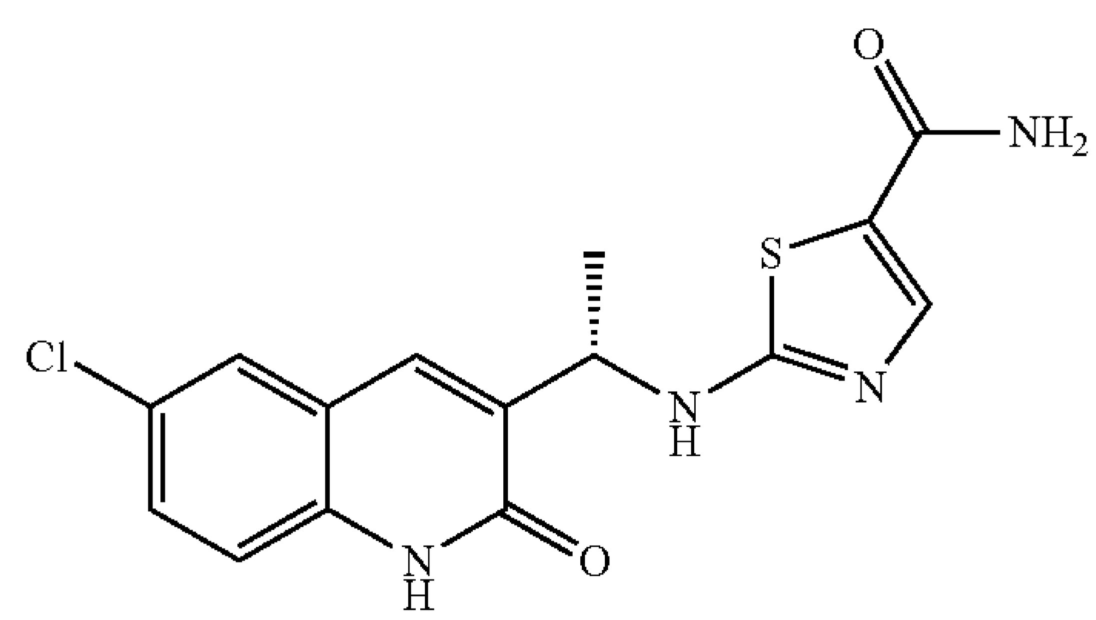
I-8



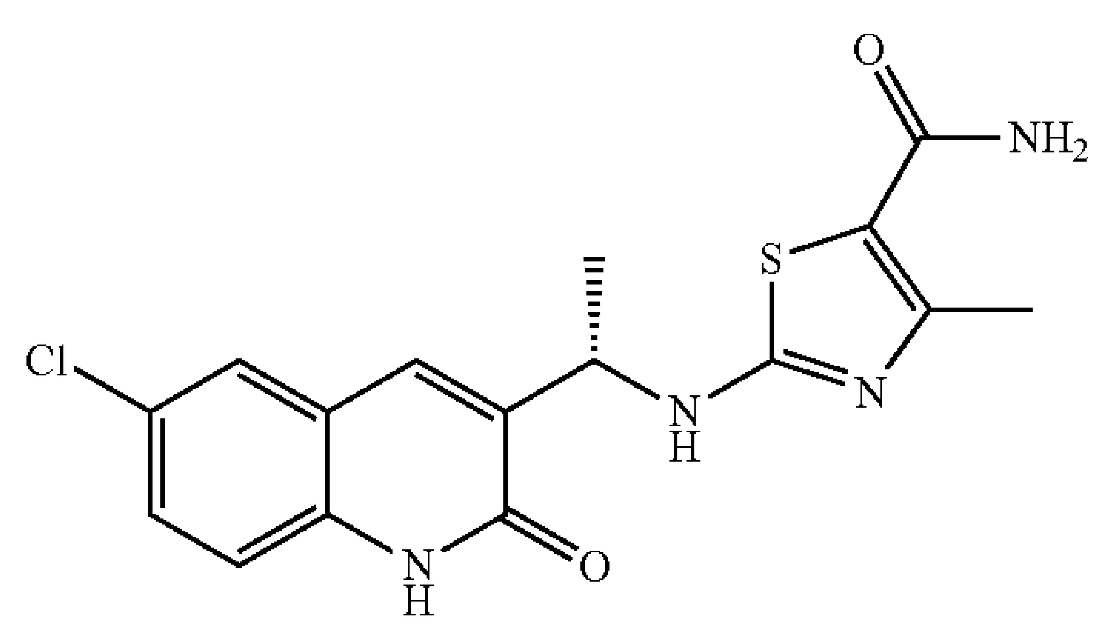
I-9



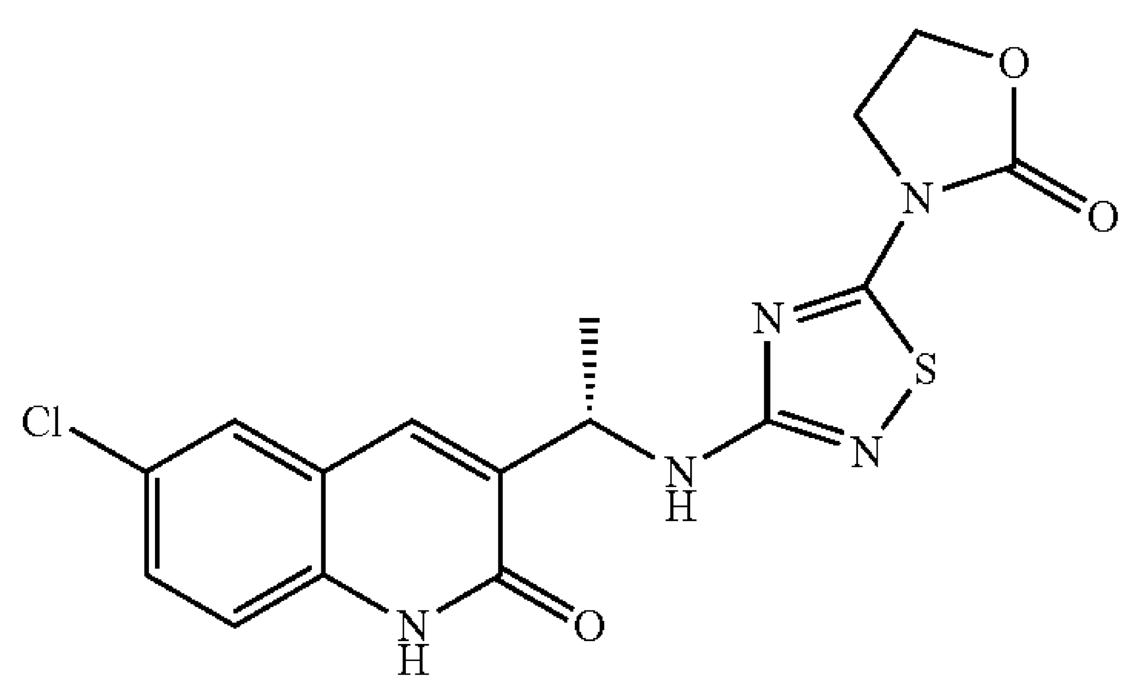
I-10



I-11

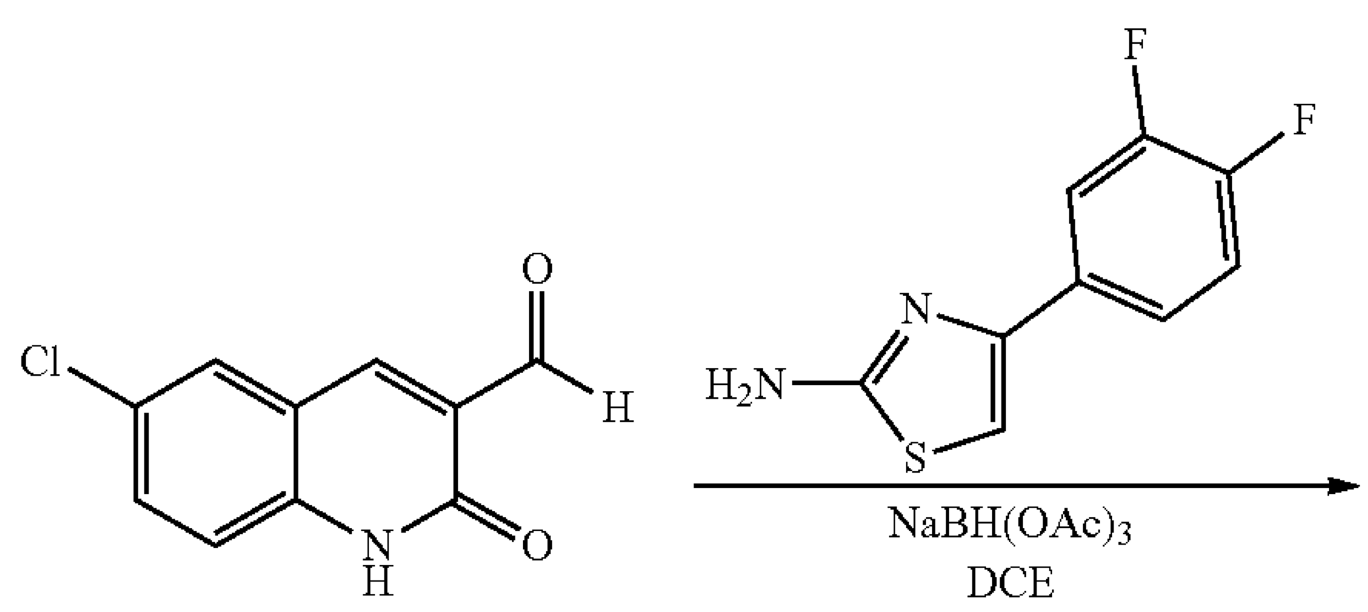


I-12

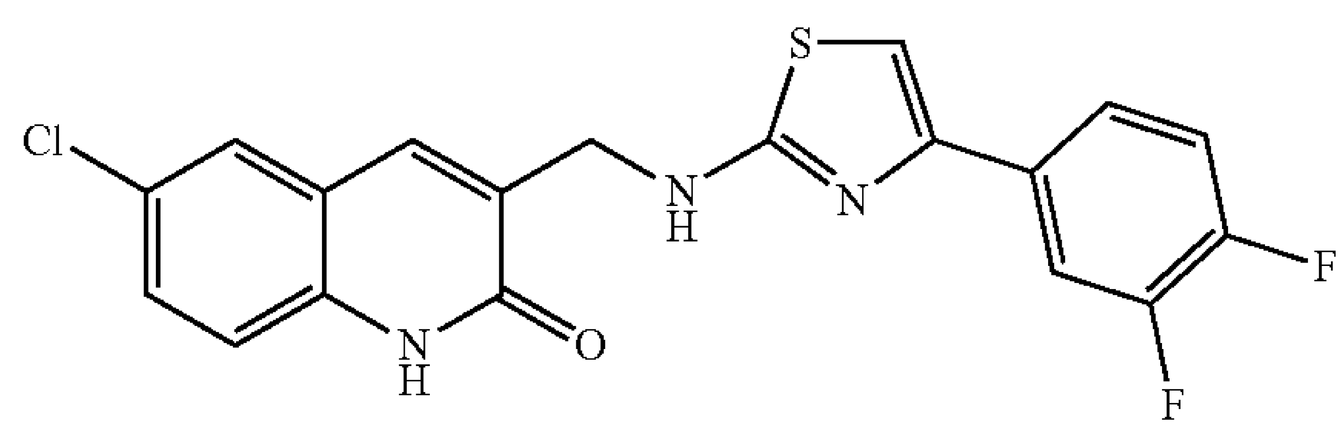


Example 25—6-Chloro-3-(((4-(3,4-difluorophenyl)thiazol-2-yl)amino)methyl)quinolin-2(1H)-one (I-14)

Scheme-4



IV



I-14

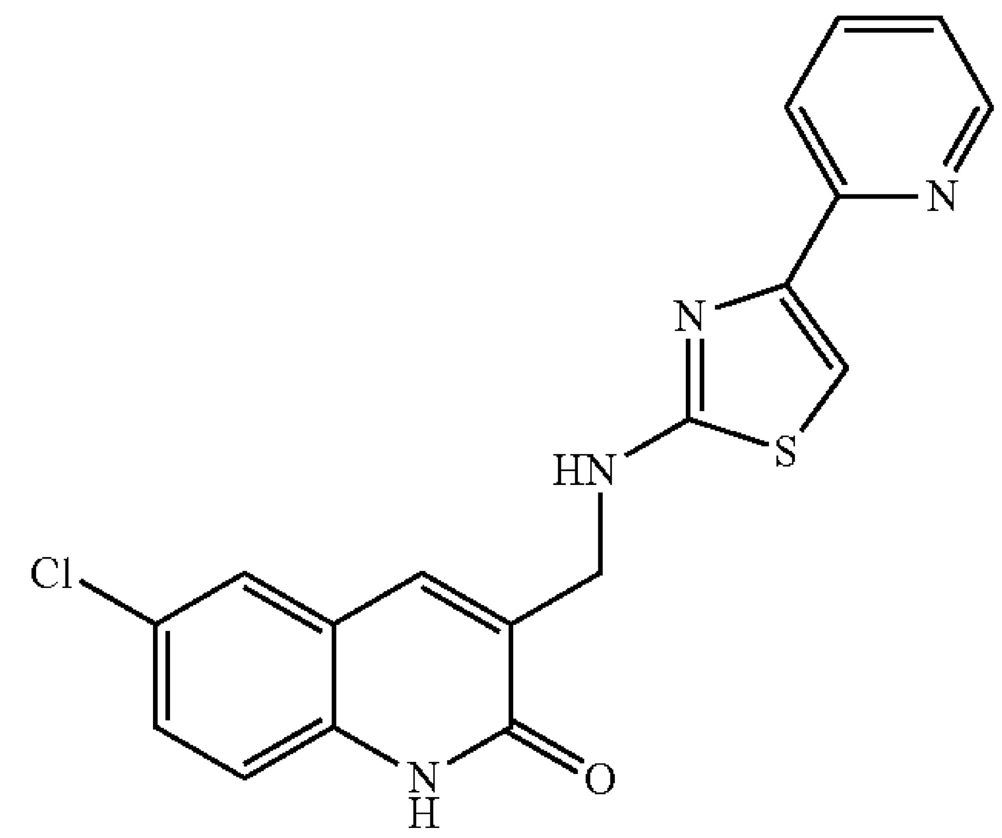
Library Protocol A;

6-Chloro-2-oxo-1,2-dihydroquinoline-3-carb aldehyde IV (6.2 mg, 30 umol) was added as a solid to a 0.2M solution of 4-(3,4-difluorophenyl)thiazol-2-amine in DMA (165 uL, 33 umol). An additional volume of 1,2-dichloroethane (150 mL) was added, and the mixture was agitated at room temperature for 5 minutes. The resultant mixture was charged with a 0.2M suspension of sodium triacetoxyborohydride in DCE (300 uL, 60 umol) and was agitated overnight at room temperature. After LC-MS analysis confirmed the presence of reductive amination product, the mixture was concentrated under reduced pressure to remove volatile liquids. The residue was partitioned between ethyl acetate (500 uL) and saturated aqueous sodium bicarbonate solution (500 uL). The organic layer was transferred, and the aqueous layer was extracted once more with fresh ethyl acetate (500 uL). The organic layers were combined and concentrated under reduced pressure with heat (50° C.). The crude residue was dissolved in DMSO (500 uL) and purified by mass-triggered preparatory HPLC to yield the title compound 14 (2.2 mg, 18% yield). LC-MS (method 4): Rt 1.64 min, m/z 403.96 $[M+H]^+$.

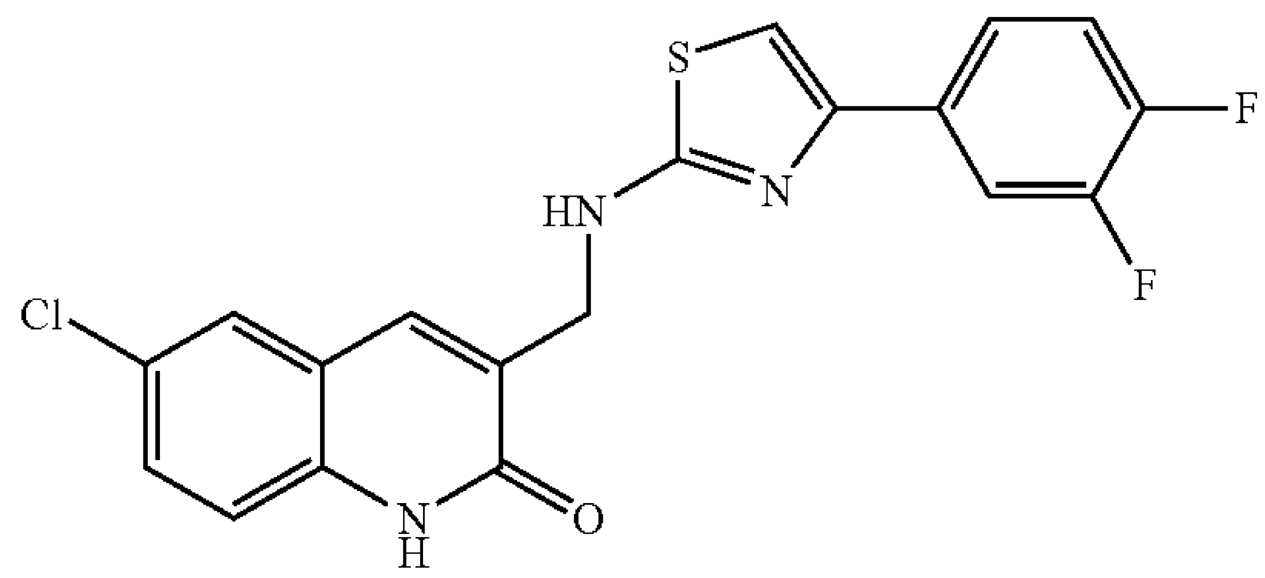
TABLE 3

The compounds listed in Table 3 were prepared using methods similar to the one described for the preparation of I-14.

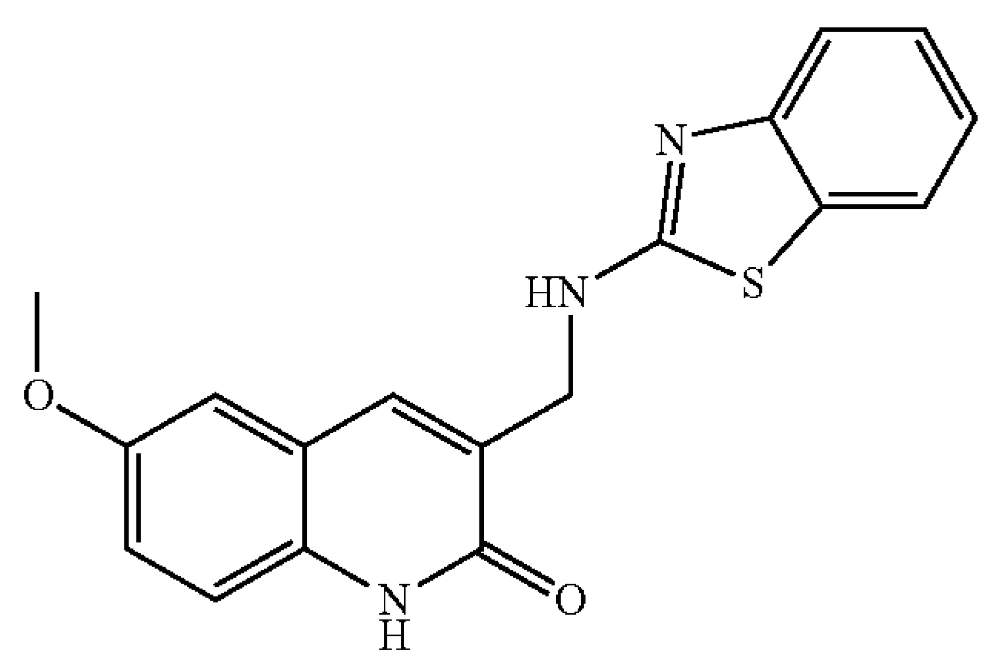
I-13



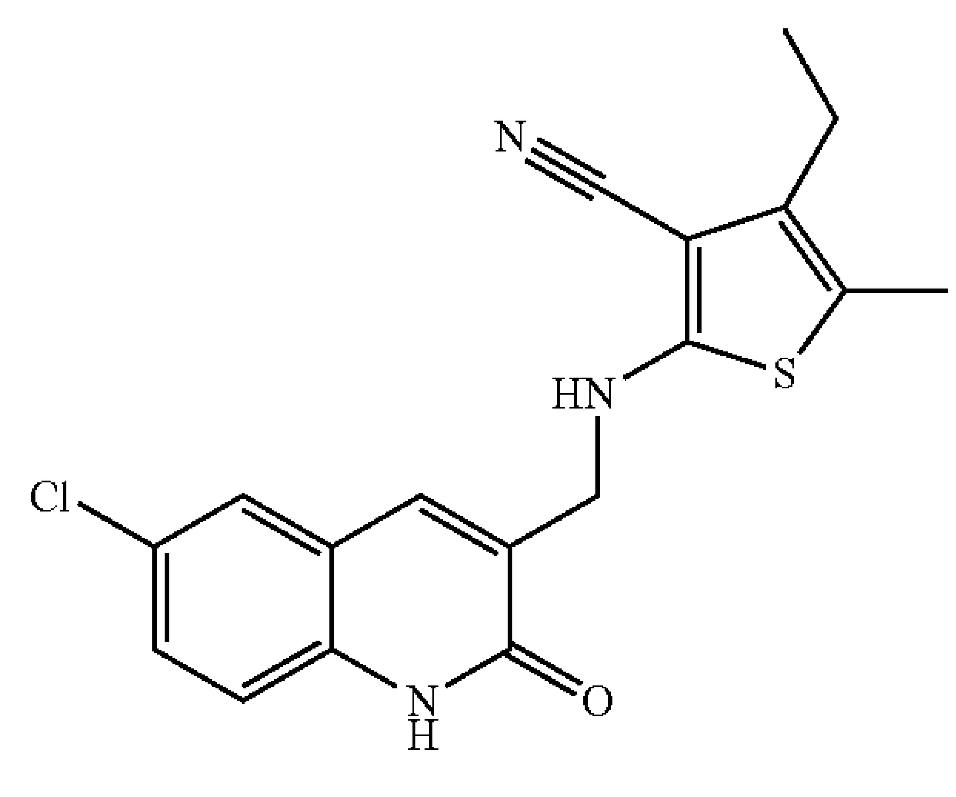
I-14



I-15



I-16



I-17

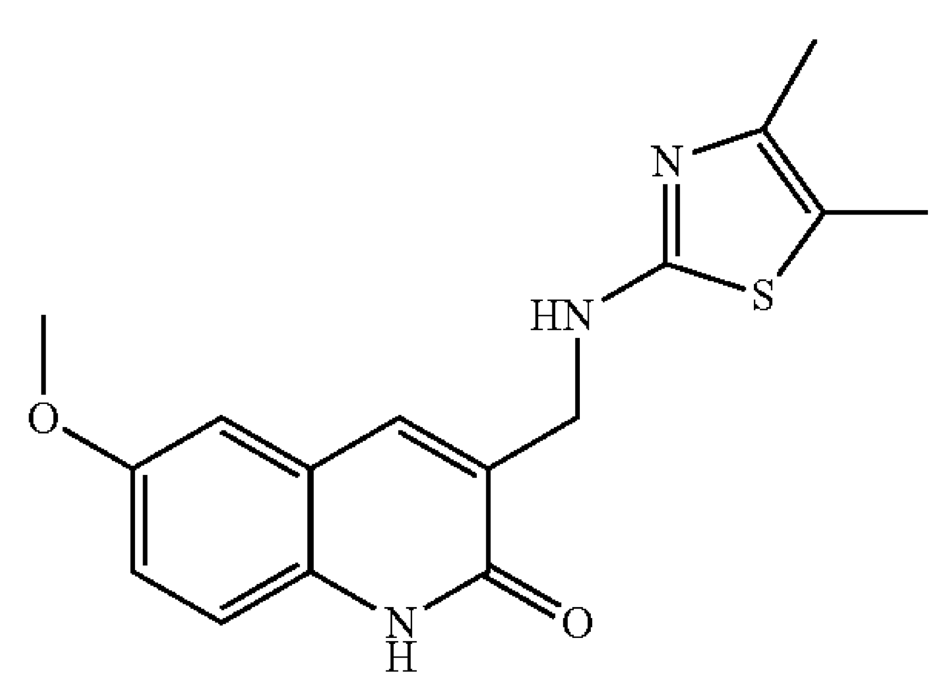


TABLE 4

LCMS signal and chemical names of each compound listed in Table 3.		
Compounds No.	LCMS	Chemical Name
I-13	m/z: 368.97 (M + H)+ Rt (min): 1.06	6-chloro-3-({[4-(pyridin-2-yl)-1,3-thiazol-2-yl]amino}methyl)-1,2-dihydroquinolin-2-one
I-14	m/z: 403.96 (M + H)+ Rt (min): 1.64	6-chloro-3-({[4-(3,4-difluorophenyl)-1,3-thiazol-2-yl]amino}methyl)-1,2-dihydroquinolin-2-one
I-15	m/z: 338.14 (M + H)+ Rt (min): 1.17	3-{[(1,3-benzothiazol-2-yl)amino]methyl}-6-methoxy-1,2-dihydroquinolin-2-one
I-16	m/z: 357.91 (M + H)+ Rt (min): 1.62	2-{[(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)methyl]amino}-4-ethyl-5-methylthiophene-3-carbonitrile
I-17	m/z: 316.14 (M + H)+ Rt (min): 0.8	3-{[(dimethyl-1,3-thiazol-2-yl)amino]methyl}-6-methoxy-1,2-dihydroquinolin-2-one

Example 26—IDH1-R132H and IDH1-R132C Enzymatic Assay

Assays were performed in a 384-well black plate. An aliquot of 250 nL of compound was incubated with 10 μL of 30 nM IDH1-R132H or 10 nM IDH1-R132C recombinant protein in assay buffer (50 mM Tris pH=7.5, 150 mM NaCl, 5 mM $MgCl_2$, 0.1% (w/v) Bovine Serum Albumin, and 0.01% Triton X-100) in each well at 25° C. for 15 minutes. After the plate was centrifuged briefly, an aliquot of 10 μL of 2 mM α-ketoglutarate and 20 μM NADPH solution prepared in assay buffer was then added to each well and the reaction was maintained at 25° C. for 45 minutes. An aliquot of 10 μL of diaphorase solution (0.15 U/mL diaphorase and 30 μM Resazurin in assay buffer) was added to each well. The plate was maintained at 25° C. for 15 minutes and then read on a plate reader with excitation and emission wavelengths at 535 nm and 590 nm, respectively. The IC_{50} of a given compound was calculated by fitting the dose response curve of inhibition of NADPH consumption at a given concentration with the four parameter logistic equation.

Example 27—Cellular 2-HG Assay Using HCT116 Mutant IDH1 Cells

HCT116 isogenic IDH1-R132H and IDH1-R132C mutant cells were cultured in growth media (McCoy's 5A, 10% fetal bovine serum, 1× antibiotic-antimycotic solution and 0.3 mg/mL G418) in 5% CO_2 in an incubator at 37° C. To prepare the assay, cells were trypsinized and resuspended in assay media (McCoy's 5A with no L-glutamine, 10% fetal bovine serum, 1× antibiotic-antimycotic solution and 0.3 mg/mL G418). An aliquot of 10,000 cells/100 μL was transferred to each well of a clear 96-well tissue culture plate. The cells were incubated in 5% CO_2 at 37° C. in an incubator overnight to allow for proper cell attachment. An aliquot of 50 μL of compound containing assay media were then added to each well and the assay plate was kept in 5% CO_2 at 37° C. in an incubator for 24 hours. The media was then removed from each well and 150 μL of a methanol/water mixture (80/20 v/v) was added to each well. The plates were kept at −80° C. freezer overnight to allow for complete cell lysis. An aliquot of 125 μL of extracted supernatant was analyzed by RapidFire high-throughout-mass spectrometry (Agilent) to determine the cellular 2-HG level. The IC_{50} of a given compound was calculated by fitting the dose response curve of cellular 2-HG inhibition at a given concentration with the four parameter logistic equation

Table 5 below provides activity of each compound according to the legend that "++++" indicates an inhibition at a concentration <0.1 μM; "+++" indicates inhibition at a concentration between 0.1 μM and 1 μM of the disclosed compound; "++" indicates inhibition at a concentration from 1 μM to 10 μM of the disclosed compound; and "+" indicates inhibition at a concentration >10 μM.

TABLE 5

Results of the illustrative compounds of Formula I in IDH1-R132H, IDH1-R132C, IDH1-MS-HTC116-R132H, and IDH1-MS-HTC116-R132C assays.				
No	Enzyme IDH1 R132H IC50 (uM)	Enzyme IDH1 R132C IC50 (uM)	HCT116 IDH1 R132H IC50 (uM)	HCT116 IDH1 R132C IC50 (uM)
I-1	++++	+++	+++	+++
I-2	++++	+++	++++	+++
I-3	++++	+++	+++	++++
I-4	++++	++++	++++	++++
I-5	+++	++		
I-6	+++			
I-7	++++	+++	++++	+++
I-8	++	+		
I-9	++			
I-10	+++	++		
I-11	++++	+++	++++	+++
I-12	+			
I-13	++			
I-14	++			
I-15	+			
I-16	+			
I-17	+			

EQUIVALENTS

Those skilled in the art will recognize, or be able to ascertain, using no more than routine experimentation, numerous equivalents to the specific embodiments described specifically herein. Such equivalents are intended to be encompassed in the scope of the following claims.

The invention claimed is:

1. A pharmaceutical composition comprising a compound selected from the group consisting of:

2-{[(1S)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1,3-thiazole-5-carbonitrile,

2-{[1-(6-chloro-7-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1,3-thiazole-5-carbonitrile,

2-({1-[6-chloro-2-oxo-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-3-yl]ethyl}amino)-1,3-thiazole-5-carbonitrile,

2-{[(1S)-1-[6-chloro-2-oxo-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-3-yl]ethyl]amino}-1,3-thiazole-5-carbonitrile,

2-{[(1R)-1-[6-chloro-2-oxo-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-3-yl]ethyl]amino}-1,3-thiazole-5-carbonitrile,

2-{[1-(6-chloro-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl)ethyl]amino}-1,3-thiazole-5-carbonitrile,

2-{[(1S)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-4-methyl-1,3-thiazole-5-carbonitrile,

N-(2-{[(1S)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1,3-thiazol-5-yl)acetamide,

ethyl 2-{[(1S)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-4-methyl-1,3-thiazole-5-carboxylate,

2-{[(1S)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1,3-thiazole-5-carboxamide,
2-{[(1S)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-4-methyl-1,3-thiazole-5-carboxamide,
6-chloro-3-[(1S)-1-{[5-(2-oxo-1,3-oxazolidin-3-yl)-1,2,4-thiadiazol-3-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
6-chloro-3-({[4-(pyridin-2-yl)-1,3-thiazol-2-yl]amino}methyl)-1,2-dihydroquinolin-2-one,
6-chloro-3-({[4-(3,4-difluorophenyl)-1,3-thiazol-2-yl]amino}methyl)-1,2-dihydroquinolin-2-one,
3-{[(1,3-benzothiazol-2-yl)amino]methyl}-6-methoxy-1,2-dihydroquinolin-2-one,
2-{[(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)methyl]amino}-4-ethyl-5-methylthiophene-3-carbonitrile,
3-{[(dimethyl-1,3-thiazol-2-yl)amino]methyl}-6-methoxy-1,2-dihydroquinolin-2-one,
2-{[1-(6-chloro-7-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1,3-thiazole-5-carbonitrile,
2-{[1-(6-chloro-7-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-4-methyl-1,3-thiazole-5-carbonitrile,
2-{[1-(6-chloro-7-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-4-methoxy-1,3-thiazole-5-carbonitrile,
6-chloro-7-fluoro-3-(1-{[5-(2-oxo-1,3-oxazolidin-3-yl)-1,3-thiazol-2-yl]amino}ethyl)-1,2-dihydroquinolin-2-one,
methyl N-(2-{[1-(6-chloro-7-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1,3-thiazol-5-yl)carbamate,
2-{[1-(6-chloro-7-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-4-methyl-1,3-thiazole-5-carboxamide,
6-chloro-7-fluoro-3-(1-{[5-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl)-1,2-dihydroquinolin-2-one,
6-chloro-7-fluoro-3-(1-{[5-(5-methyl-1H-1,2,3-triazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl)-1,2-dihydroquinolin-2-one,
6-chloro-3-(1-{[5-(5-cyclopropyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl)-7-fluoro-1,2-dihydroquinolin-2-one,
6-chloro-3-(1-{[5-(5-cyclopropyl-1H-1,2,3-triazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl)-7-fluoro-1,2-dihydroquinolin-2-one,
6-chloro-7-fluoro-3-(1-{[4-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl)-1,2-dihydroquinolin-2-one,
6-chloro-7-fluoro-3-(1-{[4-(5-methyl-1H-1,2,3-triazol-1-yl)-1,3-oxazol-2-yl]amino}ethyl)-1,2-dihydroquinolin-2-one,
6-chloro-7-fluoro-3-(1-{[4-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-oxazol-2-yl]amino}ethyl)-1,2-dihydroquinolin-2-one,
6-chloro-7-fluoro-3-(1-{[4-(pyridin-3-yl)-1,3-thiazol-2-yl]amino}ethyl)-1,2-dihydroquinolin-2-one,
6-chloro-7-fluoro-3-(1-{[4-(pyridin-3-yl)-1,3-oxazol-2-yl]amino}ethyl)-1,2-dihydroquinolin-2-one,
3-{[1-(6-chloro-7-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1-methyl-1H-1,2,4-triazole-5-carboxamide,
6-chloro-3-(1-({5-[1-cyclopropyl-1H-imidazol-5-yl)-1,3-thiazol-2-yl]amino}ethyl)-7-fluoro-1,2-dihydroquinolin-2-one,
6-chloro-3-[1-({5-[1-(cyclopropylmethyl)-1H-imidazol-5-yl]-1,3-thiazol-2-yl}amino)ethyl]-7-fluoro-1,2-dihydroquinolin-2-one,

3-{[1-(6-chloro-7-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1-methyl-1H-pyrazole-5-carboxamide,
2-{[1-(6-chloro-7-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1H-imidazole-5-carboxamide,
N-(2-{[1-(6-chloro-7-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1,3-oxazol-4-yl)acetamide,
2-{[(1S)-1-(6-chloro-7-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1,3-thiazole-5-carbonitrile,
2-{[(1S)-1-(6-chloro-7-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-4-methyl-1,3-thiazole-5-carbonitrile,
2-{[(1S)-1-(6-chloro-7-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-4-methoxy-1,3-thiazole-5-carbonitrile,
6-chloro-7-fluoro-3-[(1S)-1-{[5-(2-oxo-1,3-oxazolidin-3-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
methyl N-(2-{[(1S)-1-(6-chloro-7-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1,3-thiazol-5-yl)carbamate,
2-{[(1S)-1-(6-chloro-7-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-4-methyl-1,3-thiazole-5-carboxamide,
6-chloro-7-fluoro-3-[(1S)-1-{[5-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
6-chloro-7-fluoro-3-[(1S)-1-{[5-(5-methyl-1H-1,2,3-triazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
6-chloro-3-[(1S)-1-{[5-(5-cyclopropyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-7-fluoro-1,2-dihydroquinolin-2-one,
6-chloro-3-[(1S)-1-{[5-(5-cyclopropyl-1H-1,2,3-triazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-7-fluoro-1,2-dihydroquinolin-2-one,
6-chloro-7-fluoro-3-[(1S)-1-{[4-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
6-chloro-7-fluoro-3-[(1S)-1-{[4-(5-methyl-1H-1,2,3-triazol-1-yl)-1,3-oxazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
6-chloro-7-fluoro-3-[(1S)-1-{[4-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-oxazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
6-chloro-7-fluoro-3-[(1S)-1-{[4-(pyridin-3-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
6-chloro-7-fluoro-3-[(1S)-1-{[4-(pyridin-3-yl)-1,3-oxazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
3-{[(1S)-1-(6-chloro-7-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1-methyl-1H-1,2,4-triazole-5-carboxamide,
6-chloro-3-[(1S)-1-{[5-(1-cyclopropyl-1H-imidazol-5-yl)-1,3-thiazol-2-yl]amino}ethyl]-7-fluoro-1,2-dihydroquinolin-2-one,
6-chloro-3-[(1S)-1-({5-[1-(cyclopropylmethyl)-1H-imidazol-5-yl]-1,3-thiazol-2-yl}amino)ethyl]-7-fluoro-1,2-dihydroquinolin-2-one,
3-{[(1S)-1-(6-chloro-7-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1-methyl-1H-pyrazole-5-carboxamide,
2-{[(1S)-1-(6-chloro-7-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1H-imidazole-5-carboxamide,
N-(2-{[(1S)-1-(6-chloro-7-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1,3-oxazol-4-yl)acetamide,
2-{[(1R)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1,3-thiazole-5-carbonitrile,

2-{[(1R)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-4-methyl-1,3-thiazole-5-carbonitrile,
2-{[(1R)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-4-methoxy-1,3-thiazole-5-carbonitrile,
6-chloro-3-[(1R)-1-{[5-(2-oxo-1,3-oxazolidin-3-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
methyl N-(2-{[(1R)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1,3-thiazol-5-yl)carbamate,
2-{[(1R)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-4-methyl-1,3-thiazole-5-carboxamide,
6-chloro-3-[(1R)-1-{[5-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
6-chloro-3-[(1R)-1-{[5-(5-methyl-1H-1,2,3-triazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
6-chloro-3-[(1R)-1-{[5-(5-cyclopropyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
6-chloro-3-[(1R)-1-{[5-(5-cyclopropyl-1H-1,2,3-triazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
6-chloro-3-[(1R)-1-{[4-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
6-chloro-3-[(1R)-1-{[4-(5-methyl-1H-1,2,3-triazol-1-yl)-1,3-oxazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
6-chloro-3-[(1R)-1-{[4-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-oxazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
6-chloro-3-[(1R)-1-{[4-(pyridin-3-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
6-chloro-3-[(1R)-1-{[4-(pyridin-3-yl)-1,3-oxazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
3-{[(1R)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1-methyl-1H-1,2,4-triazole-5-carboxamide,
6-chloro-3-[(1R)-1-{[5-(1-cyclopropyl-1H-imidazol-5-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
6-chloro-3-[(1R)-1-({5-[1-(cyclopropylmethyl)-1H-imidazol-5-yl]-1,3-thiazol-2-yl}amino)ethyl]-1,2-dihydroquinolin-2-one,
3-{[(1R)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1-methyl-1H-pyrazole-5-carboxamide,
2-{[(1R)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1H-imidazole-5-carboxamide,
N-(2-{[(1R)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1,3-oxazol-4-yl)acetamide,
2-{[(1S)-1-(6-chloro-7-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1,3-thiazole-5-carbonitrile,
2-{[(1S)-1-(6-chloro-7-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-4-methyl-1,3-thiazole-5-carbonitrile,
2-{[(1S)-1-(6-chloro-7-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-4-methoxy-1,3-thiazole-5-carbonitrile,
6-chloro-7-methoxy-3-[(1S)-1-{[5-(2-oxo-1,3-oxazolidin-3-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
methyl N-(2-{[(1S)-1-(6-chloro-7-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1,3-thiazol-5-yl)carbamate,
2-{[(1S)-1-(6-chloro-7-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-4-methyl-1,3-thiazole-5-carboxamide,
6-chloro-7-methoxy-3-[(1S)-1-{[5-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
6-chloro-7-methoxy-3-[(1S)-1-{[5-(5-methyl-1H-1,2,3-triazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
6-chloro-3-[(1S)-1-{[5-(5-cyclopropyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-7-methoxy-1,2-dihydroquinolin-2-one,
6-chloro-3-[(1S)-1-{[5-(5-cyclopropyl-1H-1,2,3-triazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-7-methoxy-1,2-dihydroquinolin-2-one,
6-chloro-7-methoxy-3-[(1S)-1-{[4-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
6-chloro-7-methoxy-3-[(1S)-1-{[4-(5-methyl-1H-1,2,3-triazol-1-yl)-1,3-oxazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
6-chloro-7-methoxy-3-[(1S)-1-{[4-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-oxazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
6-chloro-7-methoxy-3-[(1S)-1-{[4-(pyridin-3-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
6-chloro-7-methoxy-3-[(1S)-1-{[4-(pyridin-3-yl)-1,3-oxazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,
3-{[(1S)-1-(6-chloro-7-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1-methyl-1H-1,2,4-triazole-5-carboxamide,
6-chloro-3-[(1S)-1-{[5-(1-cyclopropyl-1H-imidazol-5-yl)-1,3-thiazol-2-yl]amino}ethyl]-7-methoxy-1,2-dihydroquinolin-2-one,
6-chloro-3-[(1S)-1-({5-[1-(cyclopropylmethyl)-1H-imidazol-5-yl]-1,3-thiazol-2-yl}amino)ethyl]-7-methoxy-1,2-dihydroquinolin-2-one,
3-{[(1S)-1-(6-chloro-7-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1-methyl-1H-pyrazole-5-carboxamide,
2-{[(1S)-1-(6-chloro-7-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1H-imidazole-5-carboxamide,
N-(2-{[(1S)-1-(6-chloro-7-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1,3-oxazol-4-yl)acetamide,
2-({1-[6-chloro-2-oxo-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-3-yl]ethyl}amino)-4-methyl-1,3-thiazole-5-carbonitrile,
2-({1-[6-chloro-2-oxo-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-3-yl]ethyl}amino)-4-methoxy-1,3-thiazole-5-carbonitrile,
6-chloro-3-(1-{[5-(2-oxo-1,3-oxazolidin-3-yl)-1,3-thiazol-2-yl]amino}ethyl)-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-2-one,
methyl N-[2-({1-[6-chloro-2-oxo-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-3-yl]ethyl}amino)-1,3-thiazol-5-yl]carbamate,
2-({1-[6-chloro-2-oxo-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-3-yl]ethyl}amino)-4-methyl-1,3-thiazole-5-carboxamide,
6-chloro-3-(1-{[5-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl)-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-2-one,
6-chloro-3-(1-{[5-(5-methyl-1H-1,2,3-triazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl)-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-2-one,
6-chloro-3-(1-{[5-(5-cyclopropyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl)-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-2-one,

6-chloro-3-(1-{[5-(5-cyclopropyl-1H-1,2,3-triazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl)-7-(pyridin-2-yl-methoxy)-1,2-dihydroquinolin-2-one,

6-chloro-3-(1-{[4-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl)-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-2-one,

6-chloro-3-(1-{[4-(5-methyl-1H-1,2,3-triazol-1-yl)-1,3-oxazol-2-yl]amino}ethyl)-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-2-one,

6-chloro-3-(1-{[4-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-oxazol-2-yl]amino}ethyl)-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-2-one,

6-chloro-7-(pyridin-2-ylmethoxy)-3-(1-{[4-(pyridin-3-yl)-1,3-thiazol-2-yl]amino}ethyl)-1,2-dihydroquinolin-2-one,

6-chloro-7-(pyridin-2-ylmethoxy)-3-(1-{[4-(pyridin-3-yl)-1,3-oxazol-2-yl]amino}ethyl)-1,2-dihydroquinolin-2-one,

3-({1-[6-chloro-2-oxo-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-3-yl]ethyl}amino)-1-methyl-1H-1,2,4-triazole-5-carboxamide,

6-chloro-3-(1-{[5-(1-cyclopropyl-1H-imidazol-5-yl)-1,3-thiazol-2-yl]amino}ethyl)-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-2-one,

6-chloro-3-[1-({5-[1-(cyclopropylmethyl)-1H-imidazol-5-yl]-1,3-thiazol-2-yl}amino)ethyl]-7-(pyridin-2-yl-methoxy)-1,2-dihydroquinolin-2-one,

3-({1-[6-chloro-2-oxo-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-3-yl]ethyl}amino)-1-methyl-1H-pyrazole-5-carboxamide,

2-({1-[6-chloro-2-oxo-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-3-yl]ethyl}amino)-1H-imidazole-5-carboxamide,

N-[2-({1-[6-chloro-2-oxo-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-3-yl]ethyl}amino)-1,3-oxazol-4-yl]acetamide,

2-{[(1S)-1-[6-chloro-2-oxo-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-3-yl]ethyl]amino}-4-methyl-1,3-thiazole-5-carbonitrile,

2-{[(1S)-1-[6-chloro-2-oxo-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-3-yl]ethyl]amino}-4-methoxy-1,3-thiazole-5-carbonitrile,

6-chloro-3-[(1S)-1-{[5-(2-oxo-1,3-oxazolidin-3-yl)-1,3-thiazol-2-yl]amino}ethyl]-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-2-one,

methyl N-(2-{[(1S)-1-[6-chloro-2-oxo-7-(pyridin-2-yl-methoxy)-1,2-dihydroquinolin-3-yl]ethyl]amino}-1,3-thiazol-5-yl)carbamate,

2-{[(1S)-1-[6-chloro-2-oxo-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-3-yl]ethyl]amino}-4-methyl-1,3-thiazole-5-carboxamide,

6-chloro-3-[(1S)-1-{[5-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-7-(pyridin-2-yl-methoxy)-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1S)-1-{[5-(5-methyl-1H-1,2,3-triazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-7-(pyridin-2-yl-methoxy)-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1S)-1-{[5-(5-cyclopropyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1S)-1-{[5-(5-cyclopropyl-1H-1,2,3-triazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-7-(pyridin-2-yl-methoxy)-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1S)-1-{[4-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-7-(pyridin-2-yl-methoxy)-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1S)-1-{[4-(5-methyl-1H-1,2,3-triazol-1-yl)-1,3-oxazol-2-yl]amino}ethyl]-7-(pyridin-2-yl-methoxy)-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1S)-1-{[4-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-oxazol-2-yl]amino}ethyl]-7-(pyridin-2-yl-methoxy)-1,2-dihydroquinolin-2-one,

6-chloro-7-(pyridin-2-ylmethoxy)-3-[(1S)-1-{[4-(pyridin-3-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-7-(pyridin-2-ylmethoxy)-3-[(1S)-1-{[4-(pyridin-3-yl)-1,3-oxazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

3-{[(1S)-1-[6-chloro-2-oxo-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-3-yl]ethyl]amino}-1-methyl-1H-1,2,4-triazole-5-carboxamide,

6-chloro-3-[(1S)-1-{[5-(1-cyclopropyl-1H-imidazol-5-yl)-1,3-thiazol-2-yl]amino}ethyl]-7-(pyridin-2-yl-methoxy)-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1S)-1-({5-[1-(cyclopropylmethyl)-1H-imidazol-5-yl]-1,3-thiazol-2-yl}amino)ethyl]-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-2-one,

3-{[(1S)-1-[6-chloro-2-oxo-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-3-yl]ethyl]amino}-1-methyl-1H-pyrazole-5-carboxamide,

2-{[(1S)-1-[6-chloro-2-oxo-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-3-yl]ethyl]amino}-1H-imidazole-5-carboxamide,

N-(2-{[(1S)-1-[6-chloro-2-oxo-7-(pyridin-2-ylmethoxy)-1,2-dihydroquinolin-3-yl]ethyl]amino}-1,3-oxazol-4-yl)acetamide,

2-{[(1S)-1-{6-chloro-2-oxo-7-[(1R)-1-(pyridin-2-yl)ethoxy]-1,2-dihydroquinolin-3-yl}ethyl]amino}-1,3-thiazole-5-carbonitrile,

2-{[(1S)-1-{6-chloro-2-oxo-7-[(1R)-1-(pyridin-2-yl)ethoxy]-1,2-dihydroquinolin-3-yl}ethyl]amino}-4-methyl-1,3-thiazole-5-carbonitrile,

2-{[(1S)-1-{6-chloro-2-oxo-7-[(1R)-1-(pyridin-2-yl)ethoxy]-1,2-dihydroquinolin-3-yl}ethyl]amino}-4-methoxy-1,3-thiazole-5-carbonitrile,

6-chloro-3-[(1S)-1-{[5-(2-oxo-1,3-oxazolidin-3-yl)-1,3-thiazol-2-yl]amino}ethyl]-7-[(1R)-1-(pyridin-2-yl)ethoxy]-1,2-dihydroquinolin-2-one,

methyl N-(2-{[(1S)-1-{6-chloro-2-oxo-7-[(1R)-1-(pyridin-2-yl)ethoxy]-1,2-dihydroquinolin-3-yl}ethyl]amino}-1,3-thiazol-5-yl)carbamate,

2-{[(1S)-1-{6-chloro-2-oxo-7-[(1R)-1-(pyridin-2-yl)ethoxy]-1,2-dihydroquinolin-3-yl}ethyl]amino}-4-methyl-1,3-thiazole-5-carboxamide,

6-chloro-3-[(1S)-1-{[5-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-7-[(1R)-1-(pyridin-2-yl)ethoxy]-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1S)-1-{[5-(5-methyl-1H-1,2,3-triazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-7-[(1R)-1-(pyridin-2-yl)ethoxy]-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1S)-1-{[5-(5-cyclopropyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-7-[(1R)-1-(pyridin-2-yl)ethoxy]-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1S)-1-{[5-(5-cyclopropyl-1H-1,2,3-triazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-7-[(1R)-1-(pyridin-2-yl)ethoxy]-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1S)-1-{[4-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-7-[(1R)-1-(pyridin-2-yl)ethoxy]-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1S)-1-{[4-(5-methyl-1H-1,2,3-triazol-1-yl)-1,3-oxazol-2-yl]amino}ethyl]-7-[(1R)-1-(pyridin-2-yl)ethoxy]-1,2-dihydroquinolin-2-one, 6-chloro-3-[(1S)-1-{[4-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-oxazol-2-yl]amino}ethyl]-7-[(1R)-1-(pyridin-2-yl)ethoxy]-1,2-dihydroquinolin-2-one,

6-chloro-7-[(1R)-1-(pyridin-2-yl)ethoxy]-3-[(1S)-1-{[4-(pyridin-3-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-7-[(1R)-1-(pyridin-2-yl)ethoxy]-3-[(1S)-1-{[4-(pyridin-3-yl)-1,3-oxazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

3-{[(1S)-1-{6-chloro-2-oxo-7-[(1R)-1-(pyridin-2-yl)ethoxy]-1,2-dihydroquinolin-3-yl}ethyl]amino}-1-methyl-1H-1,2,4-triazole-5-carboxamide,

6-chloro-3-[(1S)-1-{[5-(1-cyclopropyl-1H-imidazol-5-yl)-1,3-thiazol-2-yl]amino}ethyl]-7-[(1R)-1-(pyridin-2-yl)ethoxy]-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1S)-1-({5-[1-(cyclopropylmethyl)-1H-imidazol-5-yl]-1,3-thiazol-2-yl}amino)ethyl]-7-[(1R)-1-(pyridin-2-yl)ethoxy]-1,2-dihydroquinolin-2-one,

3-{[(1S)-1-{6-chloro-2-oxo-7-[(1R)-1-(pyridin-2-yl)ethoxy]-1,2-dihydroquinolin-3-yl}ethyl]amino}-1-methyl-1H-pyrazole-5-carboxamide,

2-{[(1S)-1-{6-chloro-2-oxo-7-[(1R)-1-(pyridin-2-yl)ethoxy]-1,2-dihydroquinolin-3-yl}ethyl]amino}-1H-imidazole-5-carboxamide,

N-(2-{[(1S)-1-{6-chloro-2-oxo-7-[(1R)-1-(pyridin-2-yl)ethoxy]-1,2-dihydroquinolin-3-yl}ethyl]amino}-1,3-oxazol-4-yl)acetamide,

2-{[(1S)-1-[6-chloro-7-(cyclopropylmethoxy)-2-oxo-1,2-dihydroquinolin-3-yl]ethyl]amino}-1,3-thiazole-5-carbonitrile,

2-{[(1S)-1-[6-chloro-7-(cyclopropylmethoxy)-2-oxo-1,2-dihydroquinolin-3-yl]ethyl]amino}-4-methyl-1,3-thiazole-5-carbonitrile,

2-{[(1S)-1-[6-chloro-7-(cyclopropylmethoxy)-2-oxo-1,2-dihydroquinolin-3-yl]ethyl]amino}-4-methoxy-1,3-thiazole-5-carbonitrile,

6-chloro-7-(cyclopropylmethoxy)-3-[(1S)-1-{[5-(2-oxo-1,3-oxazolidin-3-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

methyl N-(2-{[(1S)-1-[6-chloro-7-(cyclopropylmethoxy)-2-oxo-1,2-dihydroquinolin-3-yl]ethyl]amino}-1,3-thiazol-5-yl)carbamate,

2-{[(1S)-1-[6-chloro-7-(cyclopropylmethoxy)-2-oxo-1,2-dihydroquinolin-3-yl]ethyl]amino}-4-methyl-1,3-thiazole-5-carboxamide,

6-chloro-7-(cyclopropylmethoxy)-3-[(1S)-1-{[5-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-7-(cyclopropylmethoxy)-3-[(1S)-1-{[5-(5-methyl-1H-1,2,3-triazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1S)-1-{[5-(5-cyclopropyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-7-(cyclopropylmethoxy)-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1S)-1-{[5-(5-cyclopropyl-1H-1,2,3-triazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-7-(cyclopropylmethoxy)-1,2-dihydroquinolin-2-one,

6-chloro-7-(cyclopropylmethoxy)-3-[(1S)-1-{[4-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-7-(cyclopropylmethoxy)-3-[(1S)-1-{[4-(5-methyl-1H-1,2,3-triazol-1-yl)-1,3-oxazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-7-(cyclopropylmethoxy)-3-[(1S)-1-{[4-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-oxazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-7-(cyclopropylmethoxy)-3-[(1S)-1-{[4-(pyridin-3-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-7-(cyclopropylmethoxy)-3-[(1S)-1-{[4-(pyridin-3-yl)-1,3-oxazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

3-{[(1S)-1-[6-chloro-7-(cyclopropylmethoxy)-2-oxo-1,2-dihydroquinolin-3-yl]ethyl]amino}-1-methyl-1H-1,2,4-triazole-5-carboxamide,

6-chloro-3-[(1S)-1-{[5-(1-cyclopropyl-1H-imidazol-5-yl)-1,3-thiazol-2-yl]amino}ethyl]-7-(cyclopropylmethoxy)-1,2-dihydroquinolin-2-one,

6-chloro-7-(cyclopropylmethoxy)-3-[(1S)-1-({5-[1-(cyclopropylmethyl)-1H-imidazol-5-yl]-1,3-thiazol-2-yl}amino)ethyl]-1,2-dihydroquinolin-2-one,

3-{[(1S)-1-[6-chloro-7-(cyclopropylmethoxy)-2-oxo-1,2-dihydroquinolin-3-yl]ethyl]amino}-1-methyl-1H-pyrazole-5-carboxamide,

2-{[(1S)-1-[6-chloro-7-(cyclopropylmethoxy)-2-oxo-1,2-dihydroquinolin-3-yl]ethyl]amino}-1H-imidazole-5-carboxamide,

N-(2-{[(1S)-1-[6-chloro-7-(cyclopropylmethoxy)-2-oxo-1,2-dihydroquinolin-3-yl]ethyl]amino}-1,3-oxazol-4-yl)acetamide,

2-{[(1S)-1-(6-chloro-8-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1,3-thiazole-5-carbonitrile,

2-{[(1S)-1-(6-chloro-8-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-4-methyl-1,3-thiazole-5-carbonitrile,

2-{[(1S)-1-(6-chloro-8-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-4-methoxy-1,3-thiazole-5-carbonitrile,

6-chloro-8-fluoro-3-[(1S)-1-{[5-(2-oxo-1,3-oxazolidin-3-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

methyl N-(2-{[(1S)-1-(6-chloro-8-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1,3-thiazol-5-yl)carbamate,

2-{[(1S)-1-(6-chloro-8-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-4-methyl-1,3-thiazole-5-carboxamide,

6-chloro-8-fluoro-3-[(1S)-1-{[5-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-8-fluoro-3-[(1S)-1-{[5-(5-methyl-1H-1,2,3-triazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1S)-1-{[5-(5-cyclopropyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-8-fluoro-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1S)-1-{[5-(5-cyclopropyl-1H-1,2,3-triazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-8-fluoro-1,2-dihydroquinolin-2-one,

6-chloro-8-fluoro-3-[(1S)-1-{[4-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-8-fluoro-3-[(1S)-1-{[4-(5-methyl-1H-1,2,3-triazol-1-yl)-1,3-oxazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-8-fluoro-3-[(1S)-1-{[4-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-oxazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-8-fluoro-3-[(1S)-1-{[4-(pyridin-3-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-8-fluoro-3-[(1S)-1-{[4-(pyridin-3-yl)-1,3-oxazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one, 3-{[(1S)-1-(6-chloro-8-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1-methyl-1H-1,2,4-triazole-5-carboxamide,

6-chloro-3-[(1S)-1-{[5-(1-cyclopropyl-1H-imidazol-5-yl)-1,3-thiazol-2-yl]amino}ethyl]-8-fluoro-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1S)-1-({5-[1-(cyclopropylmethyl)-1H-imidazol-5-yl]-1,3-thiazol-2-yl}amino)ethyl]-8-fluoro-1,2-dihydroquinolin-2-one,

3-{[(1S)-1-(6-chloro-8-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1-methyl-1H-pyrazole-5-carboxamide,

2-{[(1S)-1-(6-chloro-8-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1H-imidazole-5-carboxamide,

N-(2-{[(1S)-1-(6-chloro-8-fluoro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1,3-oxazol-4-yl)acetamide,

2-{[(1S)-1-[6-chloro-2-oxo-7-(propan-2-yloxy)-1,2-dihydroquinolin-3-yl]ethyl]amino}-1,3-thiazole-5-carbonitrile,

2-{[(1S)-1-[6-chloro-2-oxo-7-(propan-2-yloxy)-1,2-dihydroquinolin-3-yl]ethyl]amino}-4-methyl-1,3-thiazole-5-carbonitrile,

2-{[(1S)-1-[6-chloro-2-oxo-7-(propan-2-yloxy)-1,2-dihydroquinolin-3-yl]ethyl]amino}-4-methoxy-1,3-thiazole-5-carbonitrile,

6-chloro-3-[(1S)-1-{[5-(2-oxo-1,3-oxazolidin-3-yl)-1,3-thiazol-2-yl]amino}ethyl]-7-(propan-2-yloxy)-1,2-dihydroquinolin-2-one,

methyl N-(2-{[(1S)-1-[6-chloro-2-oxo-7-(propan-2-yloxy)-1,2-dihydroquinolin-3-yl]ethyl]amino}-1,3-thiazol-5-yl)carbamate,

2-{[(1S)-1-[6-chloro-2-oxo-7-(propan-2-yloxy)-1,2-dihydroquinolin-3-yl]ethyl]amino}-4-methyl-1,3-thiazole-5-carboxamide,

6-chloro-3-[(1S)-1-{[5-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-7-(propan-2-yloxy)-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1S)-1-{[5-(5-methyl-1H-1,2,3-triazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-7-(propan-2-yloxy)-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1S)-1-{[5-(5-cyclopropyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-7-(propan-2-yloxy)-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1S)-1-{[5-(5-cyclopropyl-1H-1,2,3-triazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-7-(propan-2-yloxy)-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1S)-1-{[4-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-7-(propan-2-yloxy)-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1S)-1-{[4-(5-methyl-1H-1,2,3-triazol-1-yl)-1,3-oxazol-2-yl]amino}ethyl]-7-(propan-2-yloxy)-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1S)-1-{[4-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-oxazol-2-yl]amino}ethyl]-7-(propan-2-yloxy)-1,2-dihydroquinolin-2-one,

6-chloro-7-(propan-2-yloxy)-3-[(1S)-1-{[4-(pyridin-3-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-7-(propan-2-yloxy)-3-[(1S)-1-{[4-(pyridin-3-yl)-1,3-oxazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

3-{[(1S)-1-[6-chloro-2-oxo-7-(propan-2-yloxy)-1,2-dihydroquinolin-3-yl]ethyl]amino}-1-methyl-1H-1,2,4-triazole-5-carboxamide,

6-chloro-3-[(1S)-1-{[5-(1-cyclopropyl-1H-imidazol-5-yl)-1,3-thiazol-2-yl]amino}ethyl]-7-(propan-2-yloxy)-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1S)-1-({5-[1-(cyclopropylmethyl)-1H-imidazol-5-yl]-1,3-thiazol-2-yl}amino)ethyl]-7-(propan-2-yloxy)-1,2-dihydroquinolin-2-one,

3-{[(1S)-1-[6-chloro-2-oxo-7-(propan-2-yloxy)-1,2-dihydroquinolin-3-yl]ethyl]amino}-1-methyl-1H-pyrazole-5-carboxamide,

2-{[(1S)-1-[6-chloro-2-oxo-7-(propan-2-yloxy)-1,2-dihydroquinolin-3-yl]ethyl]amino}-1H-imidazole-5-carboxamide,

N-(2-{[(1S)-1-[6-chloro-2-oxo-7-(propan-2-yloxy)-1,2-dihydroquinolin-3-yl]ethyl]amino}-1,3-oxazol-4-yl)acetamide,

2-{[(1S)-1-(6-chloro-7-cyclopropyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1,3-thiazole-5-carbonitrile,

2-{[(1S)-1-(6-chloro-7-cyclopropyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-4-methyl-1,3-thiazole-5-carbonitrile,

2-{[(1S)-1-(6-chloro-7-cyclopropyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-4-methoxy-1,3-thiazole-5-carbonitrile,

6-chloro-7-cyclopropyl-3-[(1S)-1-{[5-(2-oxo-1,3-oxazolidin-3-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

methyl N-(2-{[(1S)-1-(6-chloro-7-cyclopropyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1,3-thiazol-5-yl)carbamate,

2-{[(1S)-1-(6-chloro-7-cyclopropyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-4-methyl-1,3-thiazole-5-carboxamide,

6-chloro-7-cyclopropyl-3-[(1S)-1-{[5-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-7-cyclopropyl-3-[(1S)-1-{[5-(5-methyl-1H-1,2,3-triazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-7-cyclopropyl-3-[(1S)-1-{[5-(5-cyclopropyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-7-cyclopropyl-3-[(1S)-1-{[5-(5-cyclopropyl-1H-1,2,3-triazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-7-cyclopropyl-3-[(1S)-1-{[4-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-7-cyclopropyl-3-[(1S)-1-{[4-(5-methyl-1H-1,2,3-triazol-1-yl)-1,3-oxazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-7-cyclopropyl-3-[(1S)-1-{[4-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-oxazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-7-cyclopropyl-3-[(1S)-1-{[4-(pyridin-3-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-7-cyclopropyl-3-[(1S)-1-{[4-(pyridin-3-yl)-1,3-oxazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

3-{[(1S)-1-(6-chloro-7-cyclopropyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1-methyl-1H-1,2,4-triazole-5-carboxamide,

6-chloro-7-cyclopropyl-3-[(1S)-1-{[5-(1-cyclopropyl-1H-imidazol-5-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-7-cyclopropyl-3-[(1S)-1-({5-[1-(cyclopropylmethyl)-1H-imidazol-5-yl]-1,3-thiazol-2-yl}amino)ethyl]-1,2-dihydroquinolin-2-one,

3-{[(1S)-1-(6-chloro-7-cyclopropyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1-methyl-1H-pyrazole-5-carboxamide, 2-{[(1S)-1-(6-chloro-7-cyclopropyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1H-imidazole-5-carboxamide,

N-(2-{[(1S)-1-(6-chloro-7-cyclopropyl-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1,3-oxazol-4-yl)acetamide,

2-{[(1S)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-4-methoxy-1,3-thiazole-5-carbonitrile,

6-chloro-3-[(1S)-1-{[5-(2-oxo-1,3-oxazolidin-3-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

methyl N-(2-{[(1S)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1,3-thiazol-5-yl)carbamate,

6-chloro-3-[(1S)-1-{[5-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1S)-1-{[5-(5-methyl-1H-1,2,3-triazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1S)-1-{[5-(5-cyclopropyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1S)-1-{[5-(5-cyclopropyl-1H-1,2,3-triazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1S)-1-{[4-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1S)-1-{[4-(5-methyl-1H-1,2,3-triazol-1-yl)-1,3-oxazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1S)-1-{[4-(5-methyl-1H-1,2,3,4-tetrazol-1-yl)-1,3-oxazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one

6-chloro-3-[(1S)-1-{[4-(pyridin-3-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1S)-1-{[4-(pyridin-3-yl)-1,3-oxazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

3-{[(1S)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1-methyl-1H-1,2,4-triazole-5-carboxamide,

6-chloro-3-[(1S)-1-{[5-(1-cyclopropyl-1H-imidazol-5-yl)-1,3-thiazol-2-yl]amino}ethyl]-1,2-dihydroquinolin-2-one,

6-chloro-3-[(1S)-1-({5-[1-(cyclopropylmethyl)-1H-imidazol-5-yl]-1,3-thiazol-2-yl}amino)ethyl]-1,2-dihydroquinolin-2-one,

3-{[(1S)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1-methyl-1H-pyrazole-5-carboxamide,

2-{[(1S)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1H-imidazole-5-carboxamide, and

N-(2-{[(1S)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1,3-oxazol-4-yl)acetamide;

or a pharmaceutically acceptable salt thereof.

2. The pharmaceutical composition of claim **1**, wherein the compound is selected from the group consisting of:

2-{[(1S)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1,3-thiazole-5-carbonitrile,

2-{[1-(6-chloro-7-methoxy-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1,3-thiazole-5-carbonitrile,

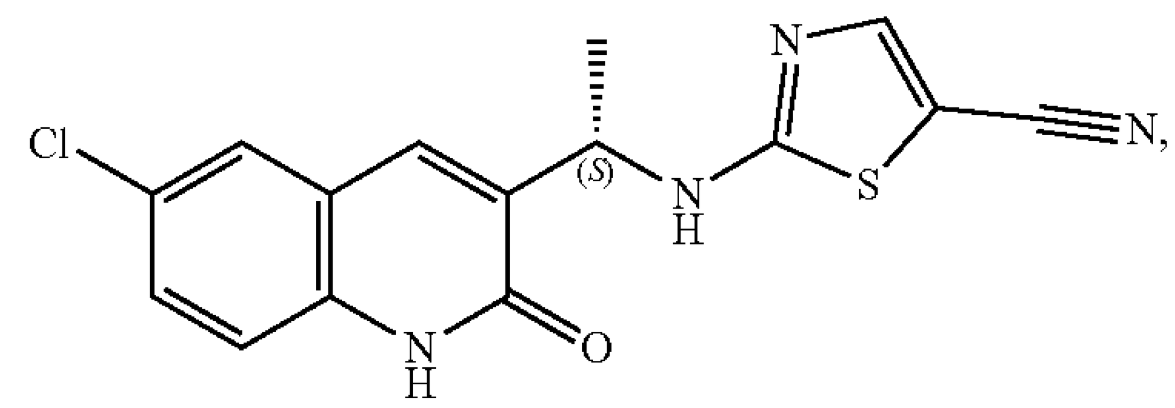
2-{[1-(6-chloro-2-oxo-1,2-dihydro-1,8-naphthyridin-3-yl)ethyl]amino}-1,3-thiazole-5-carbonitrile,

2-{[(1S)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-4-methyl-1,3-thiazole-5-carbonitrile, and

N-(2-{[(1S)-1-(6-chloro-2-oxo-1,2-dihydroquinolin-3-yl)ethyl]amino}-1,3-thiazol-5-yl)acetamide;

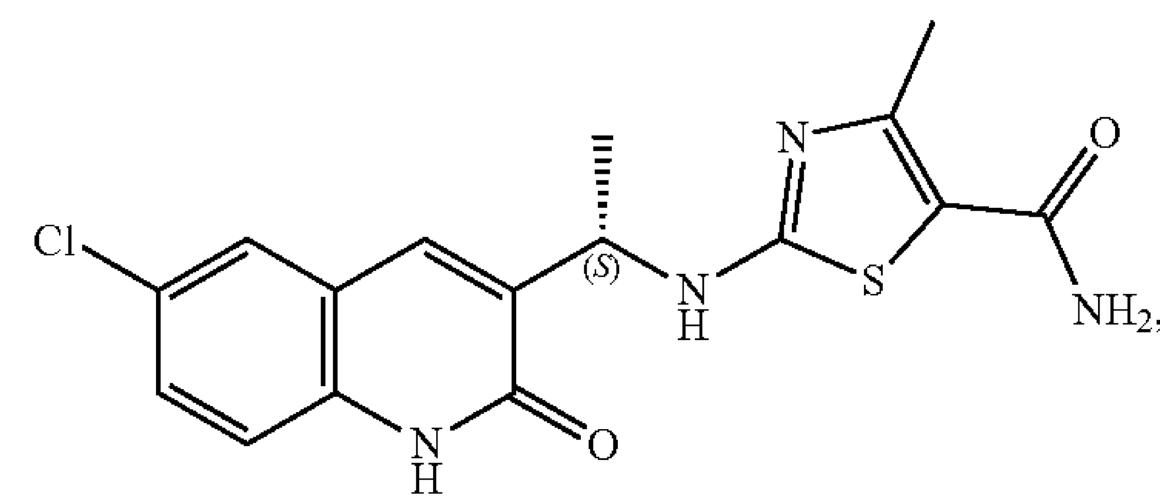
or a pharmaceutically acceptable salt thereof.

3. The pharmaceutical composition of claim **1**, wherein the compound is:



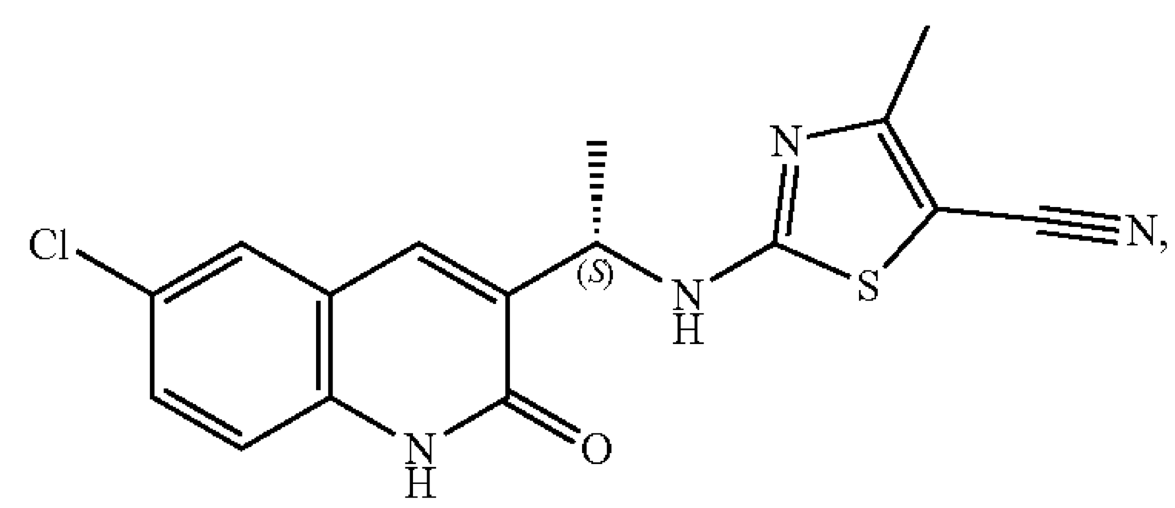
or a pharmaceutically acceptable salt thereof.

4. The pharmaceutical composition of claim **1**, wherein the compound is:



or a pharmaceutically acceptable salt thereof.

5. The pharmaceutical composition of claim **1**, wherein the compound is:



or a pharmaceutically acceptable salt thereof.

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